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THE TREATMENT OF POLYCYTHEMIA VERA WITH RADIOACTIVE PHOSPHORUS *

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PRIOR to 1941, polycythemia vera was treated in the hematology clinic at The Ohio State University, College of Medicine, by the conventional methods of venesection, x-radiation and induced hemolysis. None of these, employed either singly or in various combinations, was judged satisfactory from the viewpoint of either patient or physician, for the reasons summarized in table 1. When radioactive phosphorus (P^{32}) was first made available to us in 1941 † from the cyclotron of the Radiation Laboratory of the University of California at Berkeley, California, through the generosity of Dr. John H. Lawrence, it was decided, as our supplies permitted, to treat all patients with this disease by this newer method of therapy. At the present time, therefore, we are able to report upon our experience with radioactive phosphorus in the treatment of 108 cases of polycythemia vera from the hematologic services of Dr. B. K. Wiseman and Dr. C. A. Doan, extending over a period of almost 10 years, contrasting with an almost equal period of observation during which time 30 cases of this disease were treated by the conventional methods referred to.

THE NATURE OF POLYCYTHEMIA VERA

Polycythemia vera is far from being simply a disease in which there is an overproduction of red blood cells. Characteristically, a panmyelosis exists

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† By 1942 this supply of radiophosphorus was augmented and shortly thereafter replaced by the product of our own cyclotron. This cyclotron was donated by the late Julius F. Stone, and operated by the Department of Physics, Ohio State University furnishing material to us through the coöperation chiefly of Dr. M. L. Pool. Since late in 1946 our supply of this isotope has come from Oak Ridge, Tenn., through arrangement with the Atomic Energy Commission. This work was partially subsidized by grants from the Comly-Coleman fund.

which may easily be demonstrated upon direct examination of the bone marrow and blood, showing increased numbers of megakaryocytes, myelocytes and nucleated red blood cells per unit volume of marrow tissue, and increased numbers of blood platelets, neutrophilic leukocytes and red blood cells per unit volume of peripheral blood. Not infrequently in a given case the increase in blood platelets overshadows all other hematologic aspects of the disease and, by favoring spontaneous arterial thrombosis, dominates the clinical picture; similarly, in other cases, excessive leukocytosis with splenomegaly and hepatomegaly governs the clinical and hematologic pattern to the extent that differentiation from myeloid leukemia is difficult or even impossible.

TABLE I

Disadvantages of Conventional Methods in the Treatment of Polycythemia Vera

1. Phenylhydrazine
   A. Regulation of dosage difficult.
   B. Secondary marrow stimulation occurs.
   C. No control of platelet or white cell levels.
   D. Persistent bilirubinemia.
2. Phlebotomy
   A. Results in hypochromic polycythemia.
   B. Occasional hypoproteinemia supervenes.
   C. Secondary marrow stimulation occurs.
   D. No control of platelet or white cell levels.
   E. Unpleasant to patient.
3. Fowler's Solution
   A. Therapeutic effect requires "saturation" dosage.
   B. Control of levels of cells difficult and uncertain.
4. Nitrogen Mustards
   A. Side effects unpleasant.
   B. Treatment requires hospitalization.
   C. Control of levels of cells uncertain.
5. X-radiation
   A. X-ray sickness often severe.
   B. Considerable time and effort required.
   C. Usually expensive.

Etiologically, no causative factor to explain adequately the panmarrow stimulus of polycythemia vera has been demonstrated. There are many points of similarity with an *exceedingly chronic* type of myeloid leukemia,[1] and it is easily within the range of likelihood that, basically, chronic myeloid leukemia and polycythemia vera differ only in intensity and direction of the principal stimulus to the marrow. This hypothesis is strengthened by observations of cases of undoubted chronic lymphatic and chronic monocytic leukemia in which there was also an increase in red cell count in the peripheral blood, running often as high as 6,500,000. The primary pathology may, therefore, be that of a reticuloendotheliosis,[2] various modifying factors which are entirely unknown deciding in a given instance the exact clinical and hematologic reaction which results and determining the descriptive designation of chronic myeloid leukemia, polycythemia vera, chronic monocytic leukemia, etc., as the case may be.

Therapeutic Considerations in Polycythemia Vera

Entirely aside from the exact etiologic mechanism by which polycythemia is produced, the practical aspects of therapy, short of curative measures, are clear. Essentially, the objective is one of controlling the excessive hyperplasia of *all* the marrow elements with minimal danger, discomfort and expense to the patient. By control of blood platelet levels, the incidental morbidity in this disease of arterial thrombosis is reduced; by control of excessive leukocytosis, the attendant symptoms of excessive splenomegaly and hepatomegaly are relieved and progression to chronic myeloid leukemia is averted; by control of red blood cell levels, freedom from symptoms due to sluggish circulation may be expected. Our experience indicates that the use of radiophosphorus fulfills the hematologic and clinical requirements completely and safely, and that the low cost and freedom from discomfort attending this therapy is appreciated by the patient not only in an articulate fashion, but more importantly, by increased coöperation in returning to the clinic for reëxamination and treatment as often as advised.

Therapeutic measures other than that of irradiation fall far short of answering the optimal requirements as suggested above. As indicated in summary by table 1, neither phlebotomy nor the use of hemolytic agents controls the level of blood platelets or white cells. Actually, both methods are unphysiologic in that the continued loss of red blood cells, either by hemolysis or hemorrhage, serves as a continual additional stimulus to the erythrogenic elements, resulting in an effect exactly opposite to that which is most needed. It is true that with the onset of an iron deficiency by repeated blood-letting, the inability of the red portion of the marrow to synthesize hemoglobin adequately results in some degree of inhibition of erythrocytogenesis, but this inhibition does not extend to the megakaryocytes or myeloid cells. Additionally, the induction of marked hypochromia in the red cells often makes it impossible to maintain the hemoglobin at levels over 13 gm. per 100 c.c. of blood without allowing the red cell count to remain at polycythemic levels, i.e., not even the erythrocytosis is overcome in these instances. In the use of hemolytic agents, besides lack of control of platelet and white cell levels, regulation of dosage of lytic agents to keep the red blood cells at satisfactory levels is in most instances impossible. There is also the definite disadvantage to the patient in going about with a "muddy" complexion, an embarrassment which some patients will not tolerate.

The use of Fowler's solution as suggested by Forkner [3] has proved to be, in general, a difficult and unsatisfactory method for maintaining satisfactory adjustment of levels of cells, because therapeutic effects are usually obtainable only when the dosage is pushed to the level of arsenic intoxication. The employment of the nitrogen mustards [4, 5] has the chief disadvantage of requiring hospitalization of the patient for treatment, besides the unpleasant

side reactions of nausea and vomiting that usually accompany the administration of these drugs.

The use of deep roentgen-ray therapy (external radiation methods), given either by the spray method as recently again recommended by Richardson and Robbins,[6] or directly over the long bones as practiced in many clinics, has many points in its favor. The universal availability of suitable roentgen-ray equipment weighs heavily in its favor; however, the rapidly increasing distribution of radiophosphorus may make this of less importance. External radation technics provide for satisfactory restoration of hematologic and clinical values, important results that phlebotomy and hemolytic methods fail to achieve. However, the factors of radiation sickness and expense to the patient, as well as the time and effort of the physician, have been so important as to force this method of therapy into a secondary position. Then, too, the difficulty in accurately determining the proper total "r" in an individual case has resulted in overdosage in not a few cases. An objection to the use of both external and internal (radioisotopes given internally) radiation is the theoretic danger of inciting leukemia and/or visceral cancer. This potential hazard is discussed later. In general, it is our belief that the technics of roentgen-ray therapy in the treatment of polycythemia produce sound hematologic results, but the method, while considerably superior to the procedures of phlebotomy and lysis, is for the reasons cited to be rejected in favor of internal radiation methods.

Internal Radiation Therapy in Polycythemia Vera

The use of radioactive isotopes in the treatment of polycythemia vera has been largely confined to radiophosphorus, although certain theoretic advantages of other radioactive compounds, especially colloidal suspensions, deserve further investigation. Radiophosphorus, however, is well suited for this type of therapy since it is easily prepared, easily administered and has the proper physical, chemical and metabolic characteristics for effective and safe use in any blood dyscrasia characterized by rapidly reproducing cellular elements. Some of the more important basic principles of internal radiation treatment of polycythemia vera with radioactive phosphorus are summarized in table 2. In our experience, the oral method of administration of this substance in the fasting state has been as satisfactory as the parenteral methods, if it is assumed as standard practice that, in the fasting state and in the absence of diarrhea, 75 per cent of the administered dose will be absorbed. It has been our custom to multiply the (absorbed) dose desired in a given patient by four-thirds, giving this latter larger amount, thus "automatically" correcting for the approximately 25 per cent that will usually not be absorbed.

Point "5" in table 2 emphasizes the obvious fact that safety in the use of materials for internal radiation effects depends in substantial part upon the accuracy of standardization of radioactivity. Prior to the recommendation and unification of standardization procedures by the United States

Bureau of Standards, the unit strength of this material varied widely in the different laboratories. This long suspected "variable millicurie" was proved when the United States Bureau of Standards assembled the results of the testing on an "unknown" sample of P^{32} as phosphate ion by 48 coöperating laboratories throughout the United States. Although the majority of the testing laboratories obtained a satisfactory result of plus or minus 10 per cent of the radioactivity as measured by the Bureau of Standards, in two instances there were maximum errors of about 250 per cent. Thus it is

TABLE II

Basic Principles of Internal Radiation Therapy with Radiophosphate in the Treatment of Polycythemia Vera

1. P^{32} emits beta rays only; half-life, 14.3 days; maximum depth of penetration 0.8 cm.; average penetration in soft tissues is about 2 mm.
2. P^{32} built into nucleoprotein of cells, the same as P^{31}; highest concentration in rapidly multiplying cells and in bones and teeth as insoluble phosphates.
3. 1 mC P^{32} in 24 hrs. in 70 kg. adult irradiation equivalent to about 0.6 r total body x-ray the first day, or about 12 r during the time required for the complete decay of the P^{32}, neglecting loss by excretion.[16]
4. Administration:
   I-V: 5–25% excreted in 4 to 6 days (mostly via the urine).
   Oral: 15–50% excreted in 4 to 6 days (mostly via the stools).
   Oral: Average absorption about 75% (fasting state).
   I-V or Oral: About 1% of absorbed dose eliminated daily (mostly via urine).
   Remaining beta-radiation effect from absorbed dose at the end of:

Week	% of P^{32} Remaining (Loss Due to Radioactive Decay)	Adjusted for Loss by Excretion at the Rate of 1% per day
0	100.0	100.0
1	71.2	66.4
2	50.7	44.1
3	36.1	29.3
4	25.7	19.4
6	13.1	8.57
8	6.62	3.77
10	3.36	1.67

5. Strength of millicurie unit must be known—
   Standardization within ±10%; U. S. Bureau of Standards is essential.
6. P^{32} does not accelerate destruction of circulating red blood cells. Effect is confined to suppressing hematopoiesis in bone marrow.
7. Individual sensitivity to irradiation varies. Effect in each case must be determined in terms of red blood cells, white blood cells and platelets separately.

possible that some reports of dangerous reactions following the use of P^{32} are explained at least in part by inaccurate standardization of radioactivity. This emphasizes the importance of relating the strength of all material used to within the allowable error of plus or minus 10 per cent of the standard millicurie. The United States Bureau of Standards has now made this possible by sending to any radiation laboratory, upon request and payment of a small fee, standardized samples of radiophosphate at frequent intervals for purposes of serving as a check upon individual testing methods.

Point "6" in table 2 calls attention to the fact that the therapeutic effect

with reference to red blood cells of a given dose of radiophosphate cannot be evaluated for a period of at least two months. Radiophosphorus provides for a reduction of circulating red cells only by decreasing the rate of their formation by partial suppression of erythrogenesis. The fall in the red cell count of the peripheral blood is therefore necessarily slow and is determined chiefly by the normal physiologic loss. Since red cells have a life cycle of at least 120 days, normal attrition will not be sufficiently apparent by counts of the peripheral blood to permit evaluation of marrow suppression for at least 60 days. In doubtful cases it is necessary to depend on greater time intervals of observation. The construction of curves of red cell levels from samples obtained at bi-weekly intervals, beginning four weeks after the administration of a given dose of radiophosphate is of help in estimating maximum therapeutic effect by observing when the curve tends to flatten out. The delay in fall of red cell levels often becomes of importance in another sense. Patients with excessively high levels of red cells who require relief from symptoms may be treated satisfactorily by initial phlebotomy, either before or at any period 24 hours after the administration of radiophosphate. This combined method of therapy has been very satisfactory in our experience and is recommended as standard procedure in instances when the red cell level exceeds 7,500,000 when treatment with radiophosphate is first begun; phlebotomy is not recommended subsequently, as the stimulating effect upon the bone marrow of hemorrhage is undesirable.

Point "7" makes it clear that there are individual differences in tolerance by the bone marrow to equivalent doses of P^{32}. A few cases are so resistant to radiation effects that they are best treated by the conventional methods. Another small group is so sensitive to radiation that extraordinary care must be exercised in treatment with radiation technics; i.e., small doses should be used at greater intervals of time than the average case requires. It is emphasized that evaluation of retreatment needs must also be considered in terms of the effect on each of the circulating blood elements, and not the level of red blood cells alone.

Effect of Radiophosphorus Treatment on the Symptoms and Signs of Polycythemia Vera

Reference to table 3 shows the most common symptoms and table 4 the most common physical signs recorded in the case histories of our series of 108 patients both before and after treatment with P^{32}. Table 3 shows that nearly all patients received complete relief of all symptoms except that of pruritus. However, even here, a substantial majority were freed from this distressing complaint. As indicated, at least 80 per cent of the patients are restored subjectively to normal and most of the remainder to near normal. With the exception of pruritus, complete failures are exceedingly uncommon.

Table 4 shows that the physical signs of this disease are uniformly treated successfully with radiophosphate. Splenomegaly is shown to be the

TABLE III

Effect of P^{32} Therapy on Symptoms, 108 Cases of Polycythemia Vera

Symptom	No. of Pts. with Symptom	% of Pts. Partly Relieved	% of Pts. Completely Relieved	% Failures
Fatigability	51	3.9	96.1	0
Headache	34	11.7	85.4	2.9
Vertigo	43	9.3	88.4	2.3
Bone pain	3	23.0	77.0	0
Pruritus	24	20.8	62.6	16.6

most difficult sign to erase completely. This may be due to permanence of enlargement of this organ from infarctions occurring previous to irradiation treatment or possibly, in some cases, to the advent of myelosclerosis. In general, extremely few patients show any physical signs of their disease after adequate radiation therapy with radiophosphate ion.

Effect of Radiophosphorus Treatment on the Hematologic Picture in Polycythemia Vera

Reference to table 5 shows the distribution of the circulating blood elements in our series of 108 cases of polycythemia vera both before and after treatment with radiophosphate. As indicated, the excess of circulating elements is controlled in nearly all of the cases in this series. An appreciable number of cases (10.8 per cent) shows a reduction of white cell count below 4,000 per cu. mm. of blood, but in no instance has the leukopenia been below 2,500 or resulted in any adverse effect upon the patient. Thrombocytopenia, defined as platelet counts below 450,000 per cu. mm. of blood (indirect method of counting), was evident in the majority of cases (86.0 per cent), but in only one case has this value been lower than 50,000, and no instances of spontaneous hemorrhage or purpura were observed. Red blood cell counts below 4,000,000 per cu. mm. of blood occurred in 69 per cent of the series, but none was below 3,000,000. It has been our impression that treatment slightly in excess so far as the red cell count is concerned is advantageous in that longer remissions are likely to be obtained.

Review of our data on the bone marrow findings before and after treatment with radiophosphate is considered inadequate to interpret satisfactorily.

TABLE IV

Effect of P^{32} Therapy on Physical Signs, 108 Cases of Polycythemia Vera

Physical Signs	No. of Patients with Sign	% of Pts. Partly Improved	% of Pts. Sign Disappeared	% Failures
Color of skin and m.m.	67	5.9	94.1	0
Conjunctival injection	41	2.4	97.6	0
Purpura and petechiae	5	0	100.0	0
Splenomegaly	66	9.0	89.5	1.5
Hepatomegaly	16	6.2	93.8	0

This is due in part to the fact that the number of cases in which the bone marrow was examined is inadequate as to number, and in part because the biopsy technic by needle aspiration often does not give reliable mathematical ratios of marrow cells. However, in 47 cases in which the marrow was examined before treatment, the marrow was judged hyperplastic with respect to all elements in 72.4 per cent, with only 12.7 per cent showing increase mainly in the nucleated red cells. Examination of a limited number of cases after treatment indicates that the marrow content is normal both quantitatively and qualitatively within the limits of judgment as provided by this technic.

TABLE V

Blood Counts before and after Treatment with Radiophosphorus, 108 Cases of Polycythemia Vera

R.B.C. in Millions	% of Cases Before Tr.	% of Cases After Tr.
3– 4	0	22.1
4– 5	0	46.9
5– 6	5.7	30.0
6– 7	19.4	0
7– 8	24.2	1.0
8– 9	28.3	0
9–10	9.7	0
10–11	9.7	0
11–12	3.0	0
Leukocytes in Thousands		
30+	6.7	0
20–30	21.1	0
10–20	57.7	2.7
6–10	14.5	40.6
4– 6	0	45.9
Less than 4	0	10.8
Platelets in Thousands*		
4,000–5,000	4.8	0
3,000–4,000	10.9	0
2,000–3,000	19.0	0
1,000–2,000	42.0	1.2
750–1,000	15.8	4.0
450– 750	6.6	8.8
100– 450	0.9	76.9
50– 100	0	8.2
Less than 50	0	0.9

* Indirect method of enumeration; physiologic normal is approximately 450,000 to 800,000.

Figure 1 shows the hematologic course of events graphically in an average case with average length of remission treated with initial venesection followed by administration of radiophosphate. After withdrawal of 2,000 c.c. of blood, the red cell level was brought down from 8,200,000 to 5,800,000. At this point, 4 millicuries of P^{32} were given orally as phosphate ion. Ten months later the red blood cells were reduced maximally to 4,700,000. Two years later a rise to slightly above 6,000,000 occurred. Retreatment thereafter with a small dose of P^{32} (2.5 mc.) orally at yearly intervals has been adequate to maintain the hematologic elements satisfactorily at near normal limits.

Figure 2 illustrates an average result in a case treated by a single dose of 3.5 mC of P^{32} orally, followed by venesections totalling 1,500 c.c. This chart emphasizes the importance of limited dosage when the platelet count is not elevated. Examination of this chart makes it apparent that the above

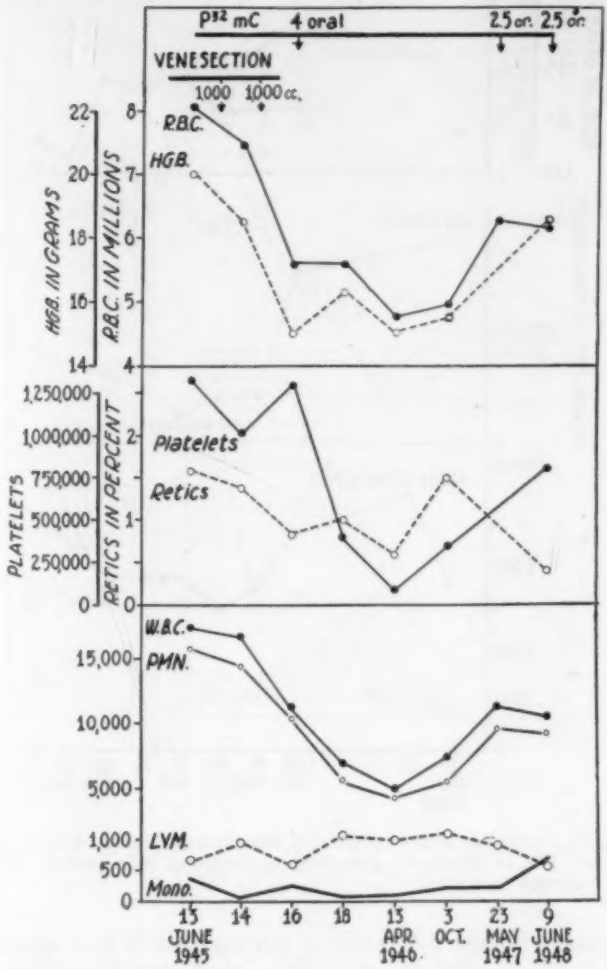

FIG. 1. A. F., aged 64 years. Pertinent hematologic values before and after treatment with 4 mC of P^{32} as phosphate orally after preliminary venesections in a patient with polycythemia vera showing a typical response to these procedures.

amount of P^{32}, while exactly correct for the control of red cell levels, was nevertheless at the borderline of safety in platelet levels. This chart also illustrates the fact, confirmed by experience in other cases, that pretreatment levels of white blood cells, if low, need not be a source of concern in estimating the dosage of P^{32} to be given. Attention is further called to the time

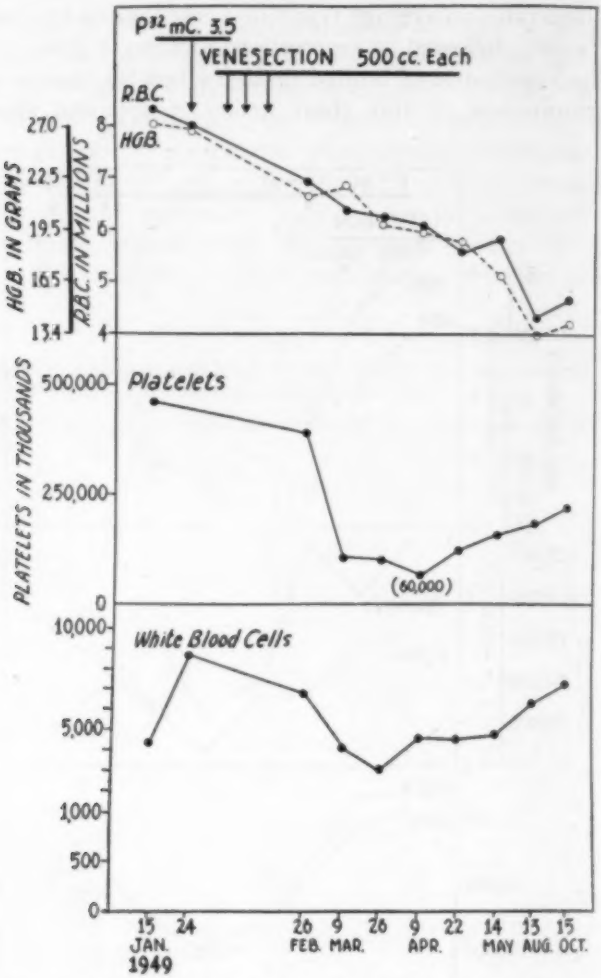

FIG. 2. L. M., aged 68 years. Pertinent hematologic values before and after treatment with 3.5 mC P^{32} as phosphate preceding venesections in a patient with polycythemia vera. Typical response is shown.

interval necessary for the red count to fall maximally in response to a single dose of this isotope. As shown, in this particular case the red cell count required seven months to fall to minimum levels, thus reëmphasizing the care that must be exerted if retreatment is undertaken at shorter intervals.

Figure 3 is reproduced to illustrate average results in a case treated solely by internal radiation, phlebotomy in this instance being impractical. This chart further shows that retreatment at intervals as short as seven weeks may not give a sufficient margin of safety in the time factor, even when treated in steadily decreasing doses. In this instance the red blood

cells were maximally reduced to 3,000,000 and the platelets to 6,980, values that represent distinct overtreatment. In this case, it required five months for the blood values to reflect maximal effects of the combined treatment on the red cells and platelets, although the base line was reached only two months after giving the last dose of radioactive material. The chart in-

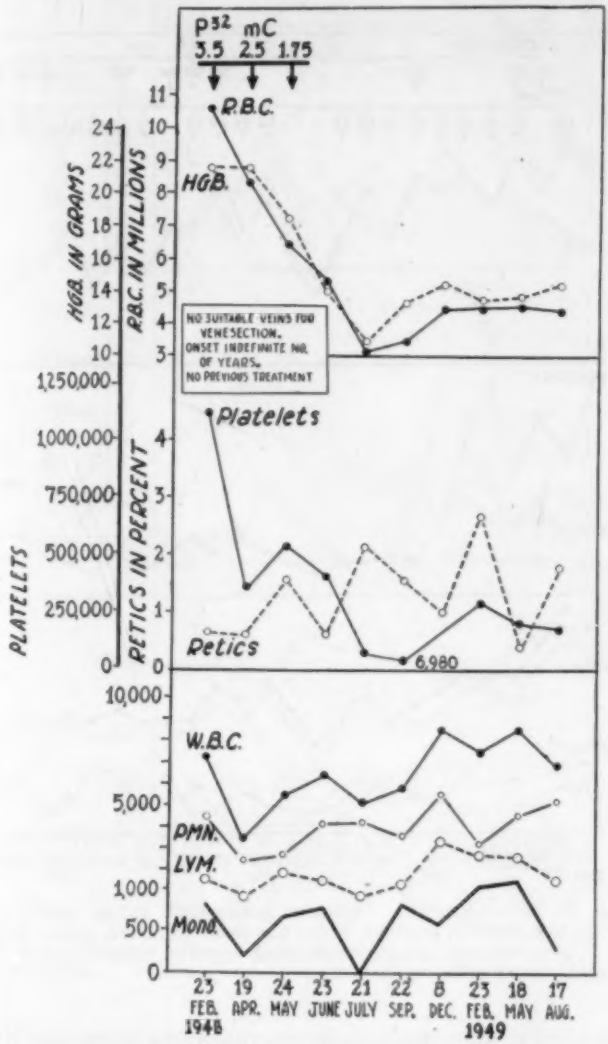

FIG. 3. M. B., aged 59 years. Pertinent hematologic values after treatment with P^{32} as phosphate orally in amounts initially of 3.5 mC, followed by 2.5 mC at intervals of 6 weeks and 5 weeks, respectively, showing the potential hazards of retreatment at intervals of less than two months. This patient should have received a single dose of 4.5 mC initially, with retreatment, if necessary, in not less than 2 months, in order to avoid the overtreatment indicated on this chart.

dicates that the final dose of P^{32} of 1.75 mC should have been omitted, with added benefit of an increase in the safety factor, even though initial platelet and red cell levels of 1,100,000 and 10.500,000, respectively, would indicate the necessity of radiophosphorus in amount larger than the average case.

Figure 4 illustrates the unsatisfactory course of the hematologic findings when attempts are made to treat this disease with doses of radiophosphate

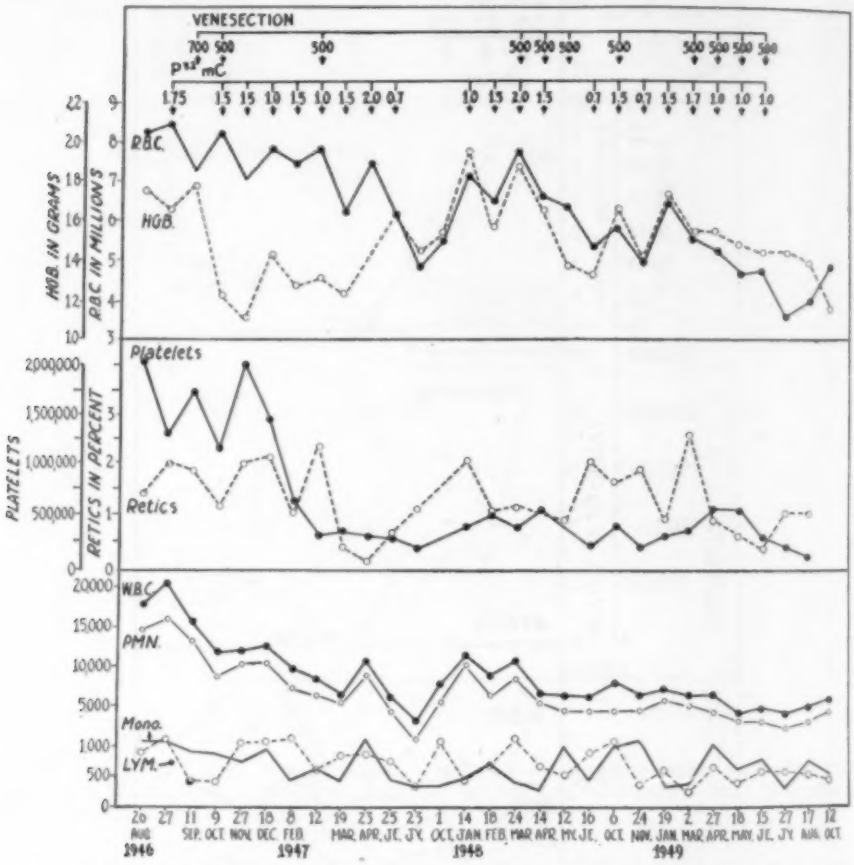

FIG. 4. M. D., aged 65 years. Pertinent hematologic values before and after treatment with P^{32} as phosphate in multiple doses, too small to obtain suppressive effects on the bone marrow. Treatment was unsatisfactory and required supplementary venesections for control of levels of blood cells.

too small to obtain immediate suppressive effects upon the hyperplasia in the bone marrow, even when the material is given frequently. This patient received a total of 28.5 mC of P^{32} over a period of three years without obtaining a satisfactory remission, necessitating intermittent venesections in order to keep the red cell count within reasonable limits. About one-seventh of

this total amount, if given in a single dose, is ordinarily adequate to induce a remission of at least two years. It is therefore clear that proper treatment of polycythemia vera with radioactive phosphorus cannot be accomplished by erring too much on the side of inadequate dosage for undue considerations of safety.

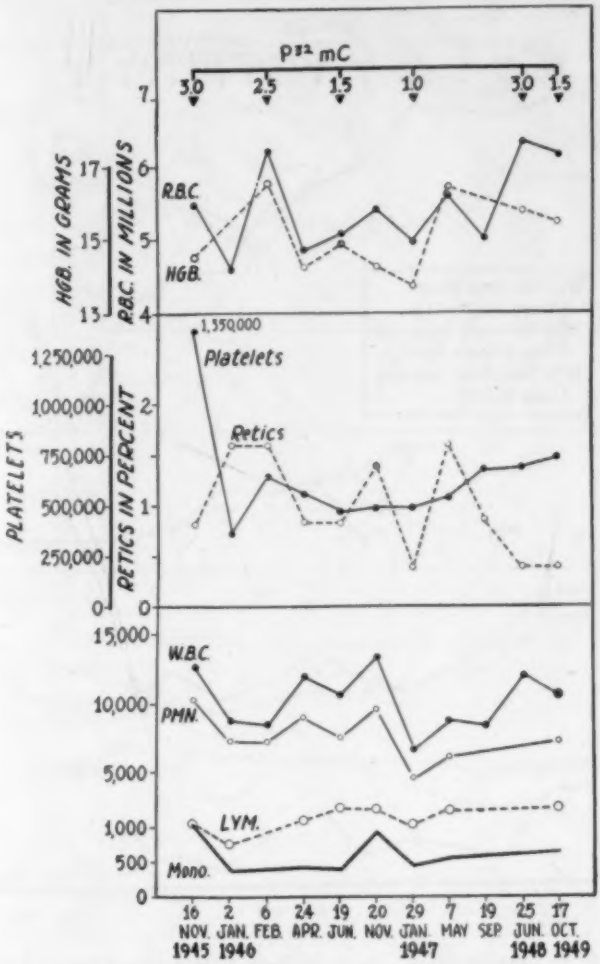

FIG. 5. W. M., aged 62 years. Pertinent hematologic values in a case of polycythemia vera in which treatment was required for control only of the blood platelet levels.

Figure 5 illustrates by case study our contention that treatment cannot be determined solely by the level of red blood cells. This patient first came under observation immediately following a stroke, with left-sided hemiplegia. Initial blood examinations did not show red cell values greater than the accepted upper range of normal. However, studies one month subsequent to

this event (first count shown on chart) established the diagnosis of polycythemia vera on a basis of a neutrophilic leukocytosis with a few late myelocytes, thrombocytosis, and a diffusely hyperplastic bone marrow, all without obvious explanation. Subsequently, red cell counts exceeding 6,000,000

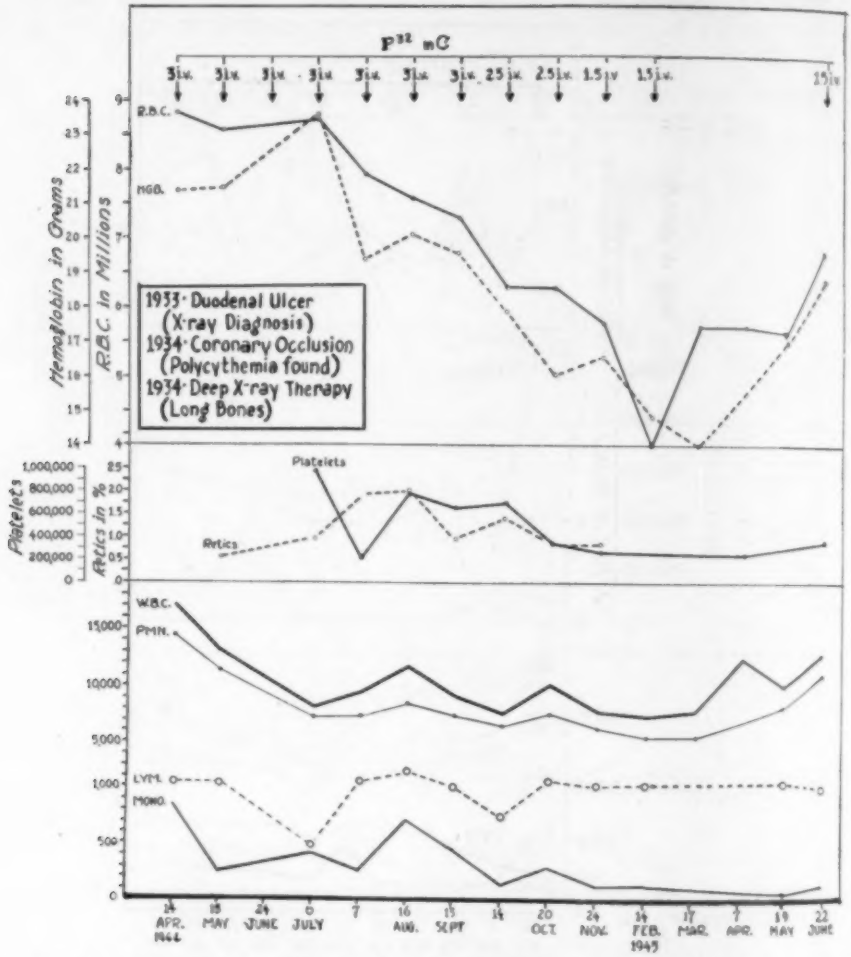

FIG. 6. H. S., aged 59 years. Pertinent hematologic values before and after treatment with P^{32} as phosphate of a partially radiation-resistant case of polycythemia vera. No worthwhile remission was obtained, although a total of 29 mC was given within a period of 10 months.

were observed even after radiophosphate therapy. This patient was therefore initially treated solely on the basis of excessive platelet levels of 1,400,000, as shown, to render less likely additional arterial occlusions, in keeping with the undoubted association of thrombocytosis and spontaneous arterial thrombosis in this disease.

Figures 6 and 7 illustrate, by case study, the fact that a few patients are too resistant to internal radiation to make this method either practical (figure 6) or possible (figure 7). The patient whose hematologic findings are shown graphically in figure 6 received 29 mC of P^{32} in divided doses

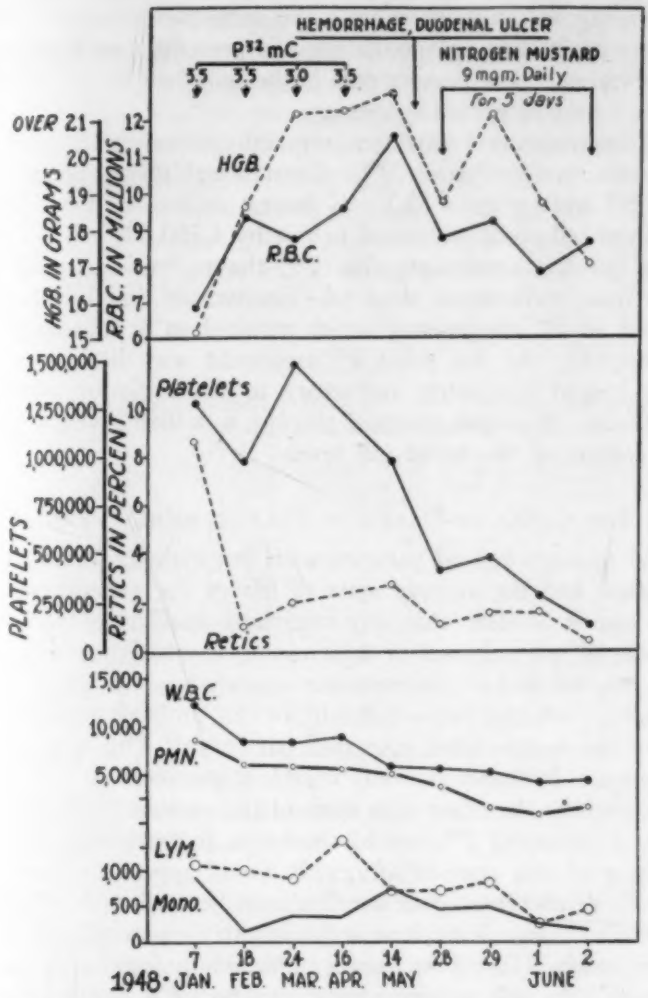

FIG. 7. E. L. M., aged 67 years. Pertinent hematologic values in a case of polycythemia vera totally radiation-resistant to the radiation effect of P^{32}. Note that the red cell count actually increased under rather heavy exposure.

intravenously over a period of 10 months before satisfactory reduction of red cell values was obtained. However, in spite of this huge accumulated dose, remission was obtained for only three months, necessitating retreatment. Treatment with P^{32} was abandoned in this case, as the marrow was judged

too radio-resistant for this method of therapy. This patient had received treatment with deep roentgen-ray therapy over the long bones, obtaining a three-year remission 10 years prior to our attempt to treat with P^{32}, the diagnosis having been made when the patient was hospitalized at that time for a coronary occlusion. The possibility that the previous therapy with deep roentgen-ray was associated with the subsequent radiation resistance to beta rays is an interesting speculation and presents a problem worthy of further observation. The present case is the only one in our files that had received both forms of radiation therapy.

Figure 7 illustrates total resistance, especially of the erythrogenic tissue of the bone marrow, to the effects of P^{32}. Even though therapeutically adequate amounts of P^{32} were given (13.5 mC during a three and one-half month period), the red cell count continued to rise by 4,500,000 cells. About one month after the last treatment with P^{32}, the patient sustained a severe hemorrhage from a duodenal ulcer (a circumstance that had occurred repeatedly prior to P^{32} treatment) which resulted in a subsequent red cell level of 8,000,000. At this point P^{32} treatment was discontinued, as the patient was judged completely refractory to the radiation effects of the radiophosphorus. Nitrogen mustard therapy was then given, with suitable subsequent control of the blood cell levels.

The Cause of Death in Polycythemia Vera

Since the average age of patients with polycythemia vera at onset is about 50 years, and the average span of life of the general population is about 67 years, it is clear that any statistical analysis of series of cases of this disease for the purposes of determining any lengthened or shortened longevity by any method of treatment can scarcely be convincing and is likely to be misleading. Added to the difficulty of this problem is the fact that the life history of this disease when untreated, particularly with respect to longevity, is unknown. Probably the only tenable statement that can be made in this connection is to the effect that none of the various methods of therapy currently used, including P^{32}, can be shown to *decrease* the prospective life span. In view of this state of affairs, it would appear that any indicated superiority of one treatment over another must be evaluated in terms of ease of administration, convenience, cost and safety to the patient, and efficiency of the treatment in maintaining the patient in maximum freedom from disability and symptoms. In our opinion, there can be little doubt that P^{32} is a superior form of therapy in attaining these objectives.

Pertinent to this discussion, however, is the problem of the possible relationship of internal radiation therapy in polycythemia vera to the initiation of malignant growths,[7] especially leukemia. A final complete answer to this problem cannot be made satisfactorily at this time and may never be possible. This is due not only to the factors of age discussed in the preceding paragraph, but equally perhaps to the fact that, since the birth of modern

hematology, no one seems to have had a long enough follow-up in a sufficiently large series of cases treated by the conventional methods to indicate the natural incidence of malignancy in this disease. This unsatisfactory state of affairs, however, has disappeared in the group of patients treated with P^{32} as the combined factors of a method personally acceptable to the patient and the circumstance that treatment could be obtained usually from only one clinic in one geographic area result in an opportunity to observe the patients throughout much of their subsequent life span. As a result of this satisfactory opportunity for follow-up, worthwhile statistical observations are available, at least in a preliminary sense, as to the incidence of malignancy and leukemia in the latter (P^{32} treated) group of patients.

Table 5 summarizes the causes of death in the group treated with P^{32} as reported in the literature,[8, 9, 10, 11] with the experience of our clinic added. This table shows that, of the 453 cases reported as presently or in the past under treatment with P^{32}, 8.8 per cent have died and the cause of death has

TABLE VI

Causes of Death in Polycythemia Vera in 453 Cases Treated with Radiophosphorus

Institution Reporting		No. of Cases	Deaths (Total)	Deaths, Acute Myel. Leuk.	Deaths, Carcinoma	Deaths, Aplastic Anemia	Deaths, Thrombosis	Deaths, Miscell.
Mayo Clinic, Rochester		124	6	4	0	0	1	1
U. of Calif., Berkeley		121	21	5	3	1	5	7
Wash. Univ., St. Louis		30	1	1	0	0	0	0
Mt. Sinai Hosp., N. Y.		40	1	0	0	1	0	0
Jefferson Hosp., Phila.		30	5	1	0	0	0	4
Ohio State Univ., Columbus		108	6	1	1	0	1	3
Totals	Number	453	40	12	4	2	7	15
	Per cent		8.8	2.7	0.9	0.5	1.6	3.3

been determined. About one-third of these have died of an acute form of leukemia but none has died of chronic leukemia. Although death from acute leukemia occurring in patients with polycythemia vera has been reported in the absence of radiation therapy,[12, 13] it seems very likely, based upon the infrequent observations of this form of death heretofore in this disease, that this figure represents a definite increase attributable to the use of P^{32}. However, patients treated with P^{32} are apparently no longer dying of chronic leukemia, although this termination was quite common, probably at least 20 per cent in groups not treated by radiation methods. (Series of Tinney, et al.,[14] of 12 deaths in 36 cases of polycythemia vera with duration of over five years, showed one-third of these died from myelogenous leukemia and one-third with "leukemoid" reactions.) These figures therefore indicate that the total number of patients dying from leukemia of all types is less in the P^{32} treated than in other groups. The observation that death from

chronic leukemia has disappeared with the simultaneous appearance of an apparently increased percentage of deaths from acute forms of leukemia strongly suggests that a small number of cases of chronic leukemia have been converted into the acute phase rather than that the inception *de novo* of acute leukemia has supervened. This position is strengthened by the observation that the termination of chronic leukemia, chiefly myeloid, in acute phases apparently has been more frequent since the widespread use of radiation technics of all types.

Table 6 shows that the induction of malignant changes by P^{32} therapy in visceral structures other than bone marrow does not occur, at least as a cause of death, in patients of this age range. The incidence of carcinoma of all types of less than 1 per cent as a cause of death in the P^{32} treated cases is not greater than the statistical average of the normal population for this age group.

TABLE VII

Incidence of Thrombotic Complications in Polycythemia Vera

Conventional Treatments Exclusive of X-Ray				Treated with P^{32}	
Institution Reporting	Total Cases	No. Cases of Thrombosis	Per Cent Cases of Thrombosis	No. Cases of Thrombosis	Per Cent Cases of Thrombosis
Mayo Clinic, Rochester	124	34	27.4	3	2.4
Univ. Calif., Berkeley	121	8	14.8	5	4.2
Ohio State Univ., Columbus	138*	24	17.3	3	2.7

* 108 cases subsequently treated with radiophosphate.

Deaths from arterial thrombosis do not seem to show any significant variation in the cases treated by P^{32} and those by other methods, or, as a matter of fact, the general population of this age range without polycythemia vera. This is somewhat surprising in view of the greatly increased incidence of thrombosis (other than cardiac) in cases treated with methods exclusive of that of radiation (table 7). No obvious theory appears to explain this paradox. Allen [15] has suggested that the absence of an increased incidence of coronary thrombosis in polycythemia vera is the result of the repetitive contraction of the heart muscle, which neutralizes the factor of increased stasis in the coronary vessels.

A Method for the Use of P^{32} in the Treatment of Polycythemia Vera

The proper employment of a powerful therapeutic agent such as P^{32} must include measures that will secure reasonably prompt therapeutic effects and, at the same time, not subject the patient to unnecessary radiation hazards. Our experience indicates that the standard procedure outlined in table 8 will accomplish this objective. For prompt reduction of red blood

cell levels, initial preliminary venesections are desirable to relieve quickly the congestive features of the disease. The use of "moderate" sized dosages of radioactive material is recommended, at least in the early phases of the treatment, in order to avoid overtreatment of the occasional patient who is more radio-sensitive than the average. All medication is best given orally, as it has been established that absorption, when the patient is in the proper basal state (point 3, table 8), is satisfactorily uniform at a value of 75 per cent of the administered dose. The anticipated 25 per cent loss encountered through oral therapy can easily be allowed for by multiplying the estimated absorbed dose desired by four-thirds. Intravenous methods have the disadvantages of subjecting attending personnel to additional radiation hazards, through additional handling of radioactive solutions, and of increased opportunity for spillage. Special emphasis is directed to points 5, 6 and 7 in

TABLE VIII

A Standardized Method of Treatment of Polycythemia Vera with P^{32}

1. If R.B.C. exceeds 7.5 million:
   Venesection of 1,000 c.c./48 hrs. to 6.0 million.
2. Initial dose of P^{32} (25% less for parenteral administration):
   Initial R.B.C. over 9.0 million—4.5 mC
   Initial R.B.C. over 8.0–9.0 million—4.0 mC
   Initial R.B.C. over 7.0–8.0 million—3.5 mC
   Initial R.B.C. under 7.0 million—3.0 mC
   } U. S. Bureau of Standards Strength
   Give 1 mC less than this schedule if platelet level is not elevated.
3. For oral administration:
   No food for 6 hrs. prior to P^{32} treatment.
   No food for 3 hrs. after P^{32} treatment. Encourage water ad lib.
   Discontinue Fe or PO_4 medication 24 hrs. before and after P^{32} treatment. No soft drinks.
   No P^{32} given orally if frequent stools are present.
4. Blood checked monthly for R.B.C., W.B.C. and platelets.
5. Additional P^{32} not given at intervals of less than 2 mo.
6. Amount and frequency of retreatment judged by response to first dose.
7. No P^{32} given if blood platelets <150,000 (indirect method), retics. <0.2%, W.B.C. <3,000.
8. Adequate protection of personnel necessary.

table 10, relating to retreatment of patients. We have encountered no instances of excessive thrombocytopenia, leukopenia or anemia since adopting the routine recommended in table 8. Cases that require more energetic management for control than that suggested by this table probably should be treated by measures other than radiation methods.

CONCLUSION

Radioactive phosphorus possesses distinct advantages over other methods in the treatment of polycythemia vera, as judged by almost 10 years' experience. The method is hematologically sound, effective, convenient for physician and patient, inexpensive and, with proper safeguards, presents less treatment hazard to the patient than other methods of therapy currently

employed. Overall longevity of the patient does not seem to be impaired according to factual evidence obtainable at present. A standard method of procedure for internal radiation treatment with P^{32} that has proved safe to the patient and effective in controlling the disease has been presented with illustrative case material.

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METHYL ALCOHOL POISONING *

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The purpose of this paper is to reëxamine some of the cardinal features of methyl alcohol poisoning in the light of 23 cases recently studied in an Army hospital in Korea.

Methyl alcohol (CH_3OH), properly known as methanol, and more commonly called wood alcohol, also passes under a large number of other names, such as Columbian spirit, Manhattan spirit, pyroxylic spirit, "derail" and "sterno." Methanol is an important industrial solvent and the major ingredient of many inexpensive anti-freeze preparations.

Acute or chronic poisoning may be produced by ingestion, cutaneous absorption or inhalation. Atmospheric concentrations of 0.2 per cent may cause systemic complaints [13] and pose a serious industrial problem. The erroneous use of methyl for ethyl alcohol as a skin rub, or its criminal incorporation in cheap hair tonics or hand lotions, may produce grave poisoning.[9] Most commonly, as in our cases, intoxication occurs after using it for a spirit beverage.

There is extreme variability in individual tolerance to this agent, but permanent blindness has been reported after ingestion of as little as 4 c.c.[8] and death has occurred after drinking 30 c.c.[16]

Fate of Methanol in the Body

Chronic poisoning is due to the cumulative effect made possible by slow elimination. Whereas ethyl alcohol is quickly and completely oxidized to harmless CO_2 and water, methanol is slowly and incompletely oxidized to products more toxic than the original compound. The metabolism of methanol proceeds about five times more slowly than that of ethanol.[14] About 40 per cent of the assimilated dose may be oxidized to formic acid, which is six times more toxic than methanol. This is one of the stronger organic acids, more than 10 times as strong as acetic acid.[2]

It is presumed that formaldehyde is produced in vivo from methanol oxidation, because the reaction is known to occur in vitro. Formaldehyde is 30 times more toxic than is methanol, and individuals poisoned with it may become profoundly acidotic. Formates are found in their urine.[6] However, formaldehyde has not been reported in the urine of methanol patients,[4] and the known promptness of formaldehyde reactions with protein makes its determination in the tissues almost impossible.[14]

One-third of the assimilated dose of methanol may remain in the body unaltered for 48 hours,[12] and traces may persist for a week in serious cases.[9]

* Received for publication April 5, 1949.

Twenty to 70 per cent is excreted unaltered through the lungs.[6, 16] Three per cent is excreted unaltered through the kidneys.[6]

Formic acid is also excreted through the kidneys and will reduce Fehling's solution. This reaction can produce a false test for glycosuria and, in comatose cases, contribute to an incorrect diagnosis of diabetes mellitus.

Mechanism of Poisoning

Methyl alcohol produces poisoning in two ways: (1) There is direct destruction and irritation of tissues by methanol or its products. (2) Acid-base balance is disturbed by the organic acid oxidation products of methanol.

The direct tissue toxicity is proportional to the concentration of methanol at various sites. All human cells are susceptible to the poison, but its distribution is largely proportional to the water content of the tissues. Methyl alcohol has unlimited miscibility with water but a very low solvent power for fats.[4, 9, 14]

Among all body fluids, the aqueous and vitreous of the eye have the highest percentage of water. Pooled horse aqueous is 99.6921 per cent water, and pooled horse vitreous is 99.6813 per cent water. Both of these liquids are fat-free.[8] The gastric juices follow a close second, with 99.5 per cent water.

Among the solid tissues of the body, unmedullated nervous tissue has the greatest water content, approximately 85 per cent. White matter, with its fatty myelin sheath, is 70 per cent water.

Thus it happens that intraocular fluid and unmedullated nervous tissues are sites of greatest clinical damage from methanol. Von Oettingen[14] corroborates this scheme of distribution, and has shown that in both poisoned rabbits and dogs the eyes contain greater methanol concentration than that found in any other organ analyzed.[14]

Some investigators have claimed "selective-toxicity" for certain neural structures,[1, 6, 12] and it is possible that the delicacy of highly differentiated cells contributes to the disproportionate destruction of the retina. But Friedman[4] and others[14] seem to be on firmer ground in challenging "selective toxicity," since one need search no further than the water-content of tissues to find an explanation for "susceptibility."

Autopsy findings will be discussed below, but suffice it to say at this point that the direct local action of methanol and formic acid damages the gastrointestinal tract (especially the stomach), the lungs, the kidneys, the liver, the pancreas, the brain and, most markedly, the eyes.

In addition to these local effects, and more important from the standpoint of therapy, methanol poisoning produces acidosis. This is thought to be due largely to the formation of formic acid, and perhaps secondarily to the accumulation of CO_2. The latter is a consequence of the alveolar damage of methanol. Harrop[7] has alleged that excessive amounts of lactic and

other organic acids are produced in this metabolic disturbance, although the reasons for this process are obscure. Under "Treatment and Results" (below) a possible additional factor, ketosis, is discussed.

Clinical Material

The 23 cases of methyl alcohol poisoning upon which these observations are based were soldiers or merchant seamen who had ingested "bootleg" sake. The first five of these patients died of respiratory arrest after several hours of coma. They were sporadic cases who had ingested relatively huge amounts of both ethyl and methyl alcohol. The sixth case was brought to the hospital in profound shock and died within four hours. The remaining 17 cases were all victims of the same batch of liquor that had killed the sixth patient, and were treated with alkalies. None died or sustained permanent injury. The pertinent laboratory data are contained in tables 1 and 2.

Symptoms and Signs

In general, patients who are candidates for therapy are those surviving sudden blindness and precipitous death from overwhelming doses. In common with most other observers, we found these patients seeking or being brought for medical care about 36 hours after ingestion of the methanol.

Mild cases were indistinguishable from patients suffering the aftermaths of ordinary ethyl alcoholism. The "hangover" consisted of headache, dizziness, nausea, lassitude and slight abdominal pain.

Some of the patients complained of violent epigastric pain. Other features were vomiting, delirium and various degrees of blindness.

Table 1

Admission Summary of Cases Received 36 Hours after Intoxication from Drinking Korean Liquor Containing 16 Per Cent Methyl Alcohol

A. Cases treated as out-patients in mild acidosis with negative blood methanol determinations and no acetonuria:

1 through 10	Urinary pH ranged from 5.5 to 7.5

B. Cases hospitalized in moderate acidosis but with negative blood methanol determinations:

	Urinary pH	Acetonuria	Hospitalized
11	4.0	++++	2 days
12	4.5	++	2 days
13	4.0	+++	2 days
14	5.5	++	1 day

C. Cases hospitalized in severe acidosis with positive blood methanol levels:

	Urinary pH	Acetonuria	Hospitalized	Methanol
15	4.0	+++	3 days	12.0 mg.%
16	5.0	++++	18 days	5.0 mg.%
17	3.5	++++	55 days	39.7 mg.%

D. Case dying in profound acidosis, cyanosis, and shock:

18	5.5	++++	3½ hours	15.6 mg.%

TABLE II

Blood Alcohol Determinations at Time of Death in Autopsied Cases
(See Reference 5 for Method)

Case	Methyl Alcohol	Ethyl Alcohol
A	150 mg.%	185 mg.%
B	96 mg.%	400 mg.%
C	60 mg.%	Unknown
D	60 mg.%	300 mg.%
E	45 mg.%	197 mg.%
F	15.6 mg.%	375 mg.%

Sometimes the usual symptoms of inebriation would partially clear, giving a false impression of recovery in the face of impending coma. Coma was frequently accompanied by Kussmaul breathing. Some of the patients then lapsed into a stage of cyanosis, with noisy gurgling respirations and, usually, respiratory arrest before circulatory collapse.

The distinctive odor of methyl alcohol or acetone was usually detected on the breath.

The eye findings show wide variation and are not correlated with the blood methanol level or other clinical signs or symptoms. Without exception we have found the pupils to be dilated and sluggish in response to light in serious cases. The conjunctivae were injected, and there was photophobia if the patient was sufficiently alert. A frequent complaint was reduced central vision, developing 24 hours after ingestion. This was usually in the form of a negative, central scotoma of the relative type. In more severe cases the scotomata may be absolute or multiple and may occur anywhere in the visual fields according to the particular ganglion cells or axon fibers involved. Night blindness, color impairment and yellow vision have been reported by others.[4, 8]

Generalized constriction of the visual fields is not seen in acute cases, and we found no impairment of accommodation as tested on seven surviving serious cases. The fundi may show generalized hyperemia. The disk may be hyperemic and the borders blurred due to papillitis. Here again the lack of correlation with other findings is marked. Funduscopy in one case shortly before and after death failed to reveal *any* objective change, although the pupils were widely dilated and totally unresponsive to light. Two cases admitted with definite papillitis and mild fundic hyperemia had only mild relative, negative, central scotomata on first examination, and on the following day visual acuity was 20/20 and J–1 in all eyes. Secondary optic atrophy has been described in patients whose vision had improved for four to six weeks, with eventual deep, glaucomatous-like cupping of 4 to 6 d.[10] No such changes occurred in our patients.

TREATMENT AND RESULTS

Combating the intense acidosis is the most important single feature of therapy. Between 1912 and 1920 much contradictory literature[14] came

from the field of laboratory experiment. Various animals showed highly different acid-base changes. Even after Harrop and Benedict [7] in 1920 emphasized the important rôle of acidosis in man, descriptions of therapy remained cluttered with regimens which are ineffective and sometimes contraindicated. The report of Merritt and Brown [12] in 1941, in which the authors felt alkalinization was life-saving in one case, was feebly accepted by standard textbooks. It remained for Chew [1] in 1946 to emphasize forcibly this keystone in treatment. McNally's text,[11] published in 1939, cites a collection of 725 reported cases in which 390 (54 per cent) died, 90 (12.4 per cent) were left totally blind, and 85 (11.7 per cent) were left with visual impairment. Chew, with intensive alkali treatment of 31 cases in 1945, reports five deaths (16 per cent), no total blindness, and only two cases (6.4 per cent) of mild residual visual impairment.

During the period of our first five autopsies, and prior to the epidemic of 18 cases, intensive alkali therapy was not practiced here. The latter patients, however, were managed with primary attention to acidosis. In this group there was only one death and no blindness or residual visual impairment. All of the victims were enlisted men from the same unit who had been drinking Korean sake from the same source. Samples of this beverage were examined and found to contain 16 per cent methyl alcohol. The patients were received on a Sunday morning following the Friday night drinking party. Blood methanol determinations and urinalyses were immediately done on each patient.

Ten, with only mild symptoms of intoxication and urinary pH's of 5.5 or higher, had negative blood methanol tests and no acetonuria. These patients were treated with 6 gm. of sodium bicarbonate every two hours until all urinary pH's reached 7.5. Each of these men returned to duty the following morning, and none had sequelae.

Four other cases, with mild epigastric discomfort, moderate acidosis, but negative blood methanol determinations and no subjective eye difficulties, were hospitalized for a period of two days. Admission urinalyses showed pH between 4.0 and 5.5, with 2 plus to 4 plus acetone. These patients were treated by immediate gastric lavage with 4 per cent sodium bicarbonate, and 500 c.c. of the solution were allowed to remain in the stomach. Urinalyses were repeated every two hours, and sodium bicarbonate was given in doses of 6 to 8 gm. by mouth every two hours. The patients were encouraged to eat heartily, and fluids were forced by mouth. All acetonuria permanently disappeared within 10 hours after admission. The sole ophthalmoscopic finding in this group was 2 plus hyperemia of the disks in one case, and that disappeared by the second day.

Three cases (15, 16, and 17), with serious acidosis, blurring of central vision and marked congestion of the optic disks, were hospitalized with blood methanol levels of 5, 12, and 39.7 mg. per cent, respectively. Urinary pH ranged between 3.5 and 5.0. Contrary to the statement of Voegtlin,[15]

all of our seriously ill patients showed 3 plus or 4 plus acetonuria. Although further work is necessary to clarify the point, we should like to suggest that ketosis may be an additional factor in the production of acidosis and in central nervous system depression. It is postulated that glucose may be a valuable adjunct to alkalinization. The mechanism of ketosis is speculative at present. It is possible that hepatic damage may be a factor.

Patients 16 and 17 had blurring of their disk borders. Patient 17 was comatose for an hour, and semi-comatose for 10 hours, and urine specimens were obtained by means of an indwelling catheter. Gastric lavage was performed in each case, and sodium bicarbonate given hourly by Levine tube until the patients were sufficiently coöperative to take oral medication.

Patient 17 was given 200 gm. of sodium bicarbonate in 26 hours before his urine became alkaline, although it is probable that some of the alkali was lost in the stools. Five per cent glucose in normal saline was given intravenously in doses of 3,000 c.c. daily to each patient. It is noteworthy that in patient 17 acetonuria disappeared following each daily glucose infusion for three consecutive days, only to return each night when sodium bicarbonate alone, and no glucose, was being administered.

Reducing substances were not excreted in sufficient amounts to give a positive Benedict's test at any time. Blood methanol levels in all three patients were negative on the day following admission, i.e., about 60 hours after ingestion. Cephalin flocculation tests were only 1 plus and 2 plus in patients 16 and 17, respectively. Patient 15 recovered entirely by the third day and was discharged with no eye findings. Patients 16 and 17 were discharged entirely well after hospitalization of 18 and 55 days, respectively.

The most severe case, 18, had a blood methanol level of 15.6 mg. per cent. He had previously complained of blindness, but was deeply comatose and in profound shock on admission. The urinary pH was 5.5 and Benedict's test was negative, but there was 4 plus acetonuria. Blood sugar was 123 mg. per cent. The eye grounds were negative. Intravenous plasma, glucose and saline were administered, along with oxygen by mask, but respirations ceased three and one-half hours after admission, and heart action became inaudible a few seconds later.

In treating methyl alcohol poisoning, a few other points should be borne in mind. The Levine tube may perforate an acute gastric ulcer, which may appear due to the poisoning, and the tube should not be inserted farther than the cardium. Intravenous solutions of sodium bicarbonate or sixth molar sodium lactate have been well recommended, but unfortunately were not available to us at the time. Aspiration of the trachea and administration of oxygen may be life-saving in view of the frothy bronchial secretions. Plasma seems to be the best agent in combating shock.

Stimulants such as epinephrine and coramine are only transient aids to the basic therapy. Narcotics, frequently advised in the older literature because of the abdominal pain, should be avoided because of their central

nervous system depression. The use of ethyl alcohol on the hypothesis that it displaces methyl alcohol has not been proved to be efficacious, and is contraindicated in view of its depressant action and the fact that these patients may also be severely intoxicated with ethyl alcohol at the outset.

Older clinicians have advised protecting the eyes from light during the acute intoxication or longer-lasting neural inflammation. While we have no proof that this procedure is beneficial, it would seem wise on the basis of resting any organ during a period of inflammation. We used complete occlusion until all signs of acute reaction had disappeared to ophthalmoscopic examination.

Autopsy Material

The essential pathologic findings in six autopsied cases were as follows: The brains showed edema and hyperemia. All cases showed varying degrees of gastritis, and one had multiple acute duodenal ulcers. The lungs uniformly showed varying degrees of congestion, edema, patchy atelectasis, and frothy debris within the bronchial passages. In two cases there was desquamation of bronchial epithelium, and one of these had moderate bronchopneumonia. The kidneys in four cases showed marked congestion of the glomerular tufts and cloudy swelling of the convoluted tubules. One of these had desquamation of epithelium in the collecting tubules. Five of the livers were grossly fatty and histologically contained lipoid vacuoles. There was cloudy swelling in the cord cells in two of these. In only one case was the pancreas affected. The changes consisted of mild congestion and parenchymal hemorrhage. The splenic pulp was congested in four cases.

Summary

1. Cardinal features in the mechanism, pathology, symptomatology and therapy of methyl alcohol poisoning are reviewed in the light of a series of 23 cases.

2. The two basic mechanisms of poisoning are direct chemical irritation of tissues and systemic acidosis. The former is influenced by the unlimited miscibility of methanol with water and the distribution of water in the tissues of the body.

3. Acidosis is the most important therapeutic consideration. Alkalinization should be prompt and vigorous. It is suggested that ketosis may play a rôle in acidosis and depression, and that intravenous glucose may be an important adjunct to treatment.

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ACUTE HEMORRHAGE FROM PEPTIC ULCERATION: AN ANALYSIS OF 322 CASES *

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ACUTE hemorrhage is the most common serious complication of gastroduodenal ulceration. Its incidence among those patients hospitalized for peptic ulcer is reported to be from 9 to 38 per cent.[1, 11] However, despite the frequency of the condition and the attention it has attracted, there is no universally accepted principle of management, and its lowest possible mortality has not been clearly established.

In more recent years, utilization of better diagnostic measures, larger amounts of blood for replacement, more careful attention to nutrition, and advances in surgical technics have somewhat modified the seriousness of the condition. Though employment of all these measures is made in most institutions, in some the general principle of medical management is strongly adhered to, whereas in others early operation is advocated. Even in those hospitals where both medical and surgical treatment are thought to have a sphere, there persists some uncertainty as to the exact circumstances wherein each is believed most applicable.

Study of the literature reveals a wide range of mortality statistics from bleeding peptic ulcer. This has tended to produce confusion, for similar principles of treatment often result in markedly different mortality rates in different institutions. As has been repeatedly expressed,[2, 3, 4, 5] one must conclude that students of the disease often fail to clearly define important aspects of their reported cases. Doubtless some of these aspects have a considerable influence on mortality and thus on the apparent effectiveness of any given treatment.

In order to help clarify some of the problems of the acutely bleeding ulcer, experience at the University Hospitals of Cleveland for the past 14 years (1935 to 1948, inclusive) has been closely examined. Particular attention has been given to the rôle of blood loss in the causation of death, and to whether each patient might have lived had he been treated differently. The influence of age and sex, the duration of the ulcer, site of the ulcer, previous acute bleeding episodes, and the size of the hemorrhages have been evaluated in their relation to a fatal outcome. The importance of continued bleeding after hospitalization has been given special attention. The frequent and grave complications encountered in the fatal cases have been evaluated as an influence in producing the fatalities.

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Information derived from this study is reported with the belief that it may be helpful in the overall planning of treatment of the disease.

Case Material

The records of 322 consecutive cases of proved peptic ulcer in whom acute hemorrhage occurred either immediately before or during hospitalization were studied. These 322 cases represent 21 per cent of all hospital admissions for peptic ulcer during a 14 year period (1935–1948). The diagnosis of peptic ulcer was established in all patients shortly before or after hemorrhage by roentgen, surgical or pathologic examination. The diagnosis of acute hemorrhage was established in all patients by three manifestations: first, sudden hematemesis or melena or both occurring shortly before or during hospitalization; second, the presence of anemia (less than 4,000,000 red blood cells and 70 per cent hemoglobin) within three days of the hemorrhage; third, the presence of blood in the stools, determined by gross examination and/or by a strongly positive chemical test. Eighty-nine per cent of patients had all three manifestations, and no less than two manifestations were applicable to the remaining 11 per cent.

In the case of those patients with multiple admissions for hemorrhage, data pertinent to the last admission only are recorded. In the group of 322 cases there were 244 duodenal ulcers with 22 deaths (9 per cent mortality), 62 gastric ulcers with 17 deaths (27 per cent mortality), and 16 anastomotic ulcers with four deaths (25 per cent mortality). Two hundred sixty-five cases were treated by medical means and 57 cases had some form of surgical procedure referable to the bleeding ulcers.

Age, Sex, and Race

Table 1 shows the age distribution of the 322 cases of this series with relation to the site of the ulcer and mortality. The opinion that hemorrhage from peptic ulcer is more likely to occur in older than in younger people is substantiated. Eighty-eight per cent of the deaths in this series occurred in people over 45 years of age, and the mortality from gastric ulcer is consistently higher than that from duodenal ulcer in all age groups.

Sex and race distributions among the 43 deaths very closely paralleled the sex and race distribution in the entire series of 322. Death occurred in women proportionately as frequently as in men, which is in contrast to the findings of Crohn [3] and Gray.[6] About 65 per cent of hemorrhages as well as deaths occurred in white males.

Previous Ulcer History

In this series, 17 per cent of patients had no history suggestive of peptic ulceration prior to the onset of the acute hemorrhage from which this study was made. The remainder of the patients (83 per cent) is about

TABLE I

Relation of Age to the Site of Peptic Ulceration and Mortality

		Age Groups				
		15–30	31–45	46–50	61 plus	Totals
Duodenal ulcer	Number	32	67	92	53	244
	Deaths	0	3	6	13	22
	Mortality	0%	5%	7%	25%	9%
Gastric ulcer	Number	1	11	30	20	62
	Deaths	0	1	7	9	17
	Mortality	0%	9%	23%	45%	27%
Anastomotic ulcer	Number	2	5	6	3	16
	Deaths	0	1	2	1	4
	Mortality	0%	20%	33%	33%	25%
Totals	Number	35	84	128	76	
	Deaths	0	5	15	23	
	Mortality	0%	6%	12%	31%	

equally divided between those with ulcer histories of less than five years' duration and those with ulcer histories of more than five years' duration.

Death occurred more often in patients with no history of previous ulceration (table 2). These 13 deaths are about equally divided between duodenal ulcer (six cases) and gastric ulcer (seven cases). The six deaths in patients with duodenal ulcer amounted to 27 per cent of all deaths from duodenal ulcer, and the seven deaths from gastric ulcer amounted to 41 per cent of all deaths from gastric ulcer. Judging from the pathologic description in 12 of the 13 cases, moreover, there was no preponderance of acute ulcers. Only two of the duodenal and four of the gastric ulcers were described as acute.

An important contributing factor would seem to be the frequent occurrence of serious complications among the 13 deaths. Of the seven patients who died with gastric ulcer and without a previous history, six had serious complicating disease. This was also true of two of the six cases of duodenal ulcer. Because of these diseases, ulcer symptoms might well have

TABLE II

Relation of Mortality to the Duration of Ulcer Symptoms

Duration of Ulcer History Prior to Hemorrhage	Cases		Deaths	
	Number	Per Cent	Number	Per Cent
None	55	17	13	24
Less than five years	133	42	18	14
More than five years	134	41	12	9
Total	322	100	43	13.3

gone unnoticed or, even more important, ulceration might have developed as a complication of other disease.

Repeated Acute Hemorrhage

There is still disagreement about the relative mortality from the first as compared to succeeding hemorrhage from peptic ulceration. The opinion has been expressed [6, 7, 8, 9] that a first hemorrhage is more serious than succeeding ones. On the other hand, Eads [10] states that a fatal outcome with a first hemorrhage is rare, and Goldman [11] believes there is an abrupt rise in mortality after the second bleeding episode. Wilkinson and Tracey [2] state that the first hemorrhage is no more serious than others.

Table III

Occurrence of Fatalities with Initial and Succeeding Hemorrhage

		1st Hemorrhage	2nd Hemorrhage	3rd or More Hemorrhage
Duodenal ulcer	No. Cases	152	46	46
	No. Deaths	16	2	4
	Mortality	10.5%	4.4%	8.7%
Gastric ulcer	No. Cases	50	7	5
	No. Deaths	17	0	0
	Mortality	34%	0%	0%
Anastomotic ulcer	No. Cases	4	2	10
	No. Deaths	1	2	1
	Mortality	25%	100%	10%
Total	No. Cases	206	55	61
	No. Deaths	34	4	5
	Mortality	17%	7%	8%

Of the 322 cases of this series, 116 had experienced one or more acute bleeding episodes prior to the hemorrhage from which this study was made. There were 34 deaths (17 per cent mortality) among the 206 admitted with a first hemorrhage. Of the 55 admitted with a second hemorrhage there were four deaths (7 per cent mortality), and of the 61 admitted with a third or more hemorrhages, there were five deaths (8 per cent mortality). In the total group, therefore, fatalities occurred in a greater proportion of those with a first hemorrhage than with succeeding ones.

Explanation for this seems to lie in the high mortality with an initial hemorrhage from gastric ulcer (table 3). No deaths occurred in the gastric ulcer group except with the first hemorrhage. Gastric ulcer repeatedly hemorrhaged with less frequency (20 per cent) than did duodenal ulcer (38 per cent), due probably to the fact that either the gastric ulcer is likely to heal or a fatality is registered with the first hemorrhage. There appears to be no strikingly significant difference between the first and succeeding hemorrhage as an influence on mortality from duodenal ulcer.

Severity of Hemorrhage

Considerable attention has been given to the size and rate of hemorrhage as an important influence in mortality. Welch [9] and others [4, 12] have emphasized that massive blood loss is accompanied by a higher mortality than lesser hemorrhages. In our experience as well as in the experience of others,[5, 8, 11, 13] however, there is considerable difficulty in judging, early in the course of acute bleeding, either the extent of blood loss or the likelihood of a fatal outcome. Patients are seen with a wide variety of reactions to their individual blood loss, whether it be great, moderate or even small.

Only about 50 per cent of our patients who arrived at the hospital with clinical shock had lost sufficient blood to reduce the red cell count below 2.5 million. In our experience, moreover, blood counts made within the first 24 hours of hospitalization frequently do not indicate the real extent of blood loss. In 30 patients who did not continue to lose blood after hospitalization and who received no blood by transfusion, restoration of blood plasma produced an average fall in the red cell count of a million cells during the first 72 to 96 hours of hospitalization. Therefore, if special treatment depending upon the size of hemorrhage should be carried out shortly after admission, more accurate guides than the reactions of the patient or the level of initial blood counts are needed in determining the volume of blood loss.

The hemorrhages in the cases of this series were separated into two divisions: those in which there was an estimated loss of blood, during the period of hemorrhage, less than half the blood volume (grade I), and those in which there was a loss of blood greater than half the blood volume (grade II). Loss of more than half the blood volume was estimated either by the red cell count actually falling below 2.5 million or by the assumption that it would have done so had it not been for the amount of blood transfused shortly after admission. Each 500 c.c. transfusion was estimated to provide one-half million red cells to the blood counts.

Overall figures of this study support the opinion that there is a greater mortality with the greater amount of blood lost. In the 182 cases with grade I hemorrhage there was a 5 per cent mortality, and in the 140 cases with grade II hemorrhage there was a 24 per cent mortality. Further analysis of this finding is described in the section below.

Bleeding after Hospitalization

In contrast to the ulcers which promptly stop bleeding, those that commence bleeding or produce recurrent or continuous hemorrhage after hospitalization deserve special attention. Justification for this is illustrated in table 4, for it is within this special group that a high mortality exists. Hemorrhage that begins or continues while the patient is being managed under hospital conditions would seem to have extremely serious connotations.

Among the 322 cases of this series, 86 (27 per cent) had manifestations of blood loss after hospital admission. Evidences of bleeding were (1) repetitious vomiting or passage by stool of visible blood, (2) continued low blood pressure and high pulse rate levels, (3) a secondary sudden drop of blood pressure, and (4) progressive decline in blood values despite transfusions. Every patient had one or more of these manifestations of hemorrhage, and it might be said that in our experience their proper evaluation is infinitely easier in retrospect. At the time of occurrence, any one or more of these evidences of blood loss may easily not be convincing.

Because of the high mortality (table 4) among these 86 patients who lost blood while in the hospital, we have compared them in a number of respects to the 236 who did not show such evidence of blood loss. Seventy-five per cent of those who hemorrhaged in the hospital and 58 per cent of those who did not were over 45 years of age. Sex and race did not differ

TABLE IV

Mortality of Medically Treated Cases with and without Bleeding in the Hospital and the Surgical Mortality among 27 Cases Operated on to Stop Hemorrhage

	Medical Cases						Surgical Cases		
	Without Bleeding in Hospital			With Bleeding in Hospital			Operated on to Stop Hemorrhage		
	Cases	Deaths	Mort.	Cases	Deaths	Mort.	Cases	Deaths	Mort.
Duodenal	171	2	1.2%	40	14	35%	13	4	31%
Gastric	31	1	3.2%	13	10	77%	11	3	27%
Anast.	9	0	0%	1	1	—	3	2	—
Total	211	3	1.4%	54	25	46%	27	9	33%

in the two groups. Twenty-six per cent of those who lost blood in the hospital and 14 per cent of those who did not had no history of peptic ulceration prior to hemorrhage. Sixty per cent of the hemorrhages which continued after hospitalization and 68 per cent of those which did not were a first bleeding episode.

A striking relation between the severity of hemorrhage, blood loss during hospitalization and mortality is shown in table 5. In those cases that stopped losing blood at the time of hospital admission, the severity of hemorrhage did not affect the death rate. With persistent bleeding, however, the mortality rises markedly with the greater amounts of blood loss. In the five cases who died with no bleeding in the hospital, death resulted principally from complications. Two died of postoperative complications following elective surgery, and one each from cardiac failure, cerebrovascular accident, and mediastinitis from a perforated esophagus.

Twenty-six of the 86 cases which started or continued to bleed after

hospitalization had gastric ulcers. This amounted to 42 per cent of all cases of gastric ulcer, whereas only 22 per cent of all duodenal ulcers hemorrhaged after hospital admission.

Medically Treated Cases and Analysis of Deaths

Medical treatment is intended to indicate the use of diet, medications, and such support with whole blood and blood products as the patient's condition warrants. In recent years the policy in this hospital has been to institute some form of feeding regimen immediately after vomiting has ceased. Generally, feedings of the Sippy type have been given, though a Meulengracht diet was used in some. In this series, however, it is difficult to attribute to the policy of early feeding any significant effect either upon bleeding after admission to the hospital or upon the death rate. Twenty-eight deaths occurred among the 265 medically treated cases and, of these, 20 occurred in persons who were completely unable to take oral feedings at

Table V

Relationship of Bleeding after Hospitalization and Severity of Hemorrhage to Mortality

Grade of Hemorrhage	Entire Series 322 Cases			No Hemorrhage in Hospital, 236 Cases			Hemorrhage in Hospital, 86 Cases		
	Cases	Deaths	Mort.	Cases	Deaths	Mort.	Cases	Deaths	Mort.
Grade I	182	9	5%	161	5	3.1%	21	4	19%
Grade II	140	34	24%	75	0	0%	65	34	51%
Totals	322	43	13.3%	236	5	2.1%	86	38	44%

any time because of continued vomiting, coma, or irreversible shock. One hundred forty cases were given feedings immediately after entering the hospital, and in 92, feeding was delayed. Fourteen per cent of the immediately fed group and 17 per cent of the delayed feeding group had bleeding in the hospital, with four deaths and three deaths, respectively.

Blood transfusions were generally given whenever the red blood count reached a level below three million. In more recent years this policy was liberalized so that transfusions were given with less severe anemia than a red count of three million.

The 28 cases that died while being treated medically have been carefully analyzed both clinically and pathologically. Autopsies were performed in all but three. Deaths resulted from blood loss alone in nine cases, from blood loss plus circulatory complications in six, and from blood loss plus other complications in 13. After careful study, we have concluded that death might have been avoided by early operation in six cases of duodenal ulcer and in four cases of gastric ulcer. If we can assume that all of these cases had been sucessfully operated upon, we are left with 10 deaths among 205

medically treated cases of duodenal ulcer (mortality, 5 per cent), and seven deaths among 40 medically treated cases of gastric ulcer (mortality, 17 per cent). In this series, at least, it would seem highly unlikely that these mortality ratios could have been improved upon.

The very high incidence of grave complications among the 28 deaths in these medically treated cases is shown by the fact that only nine of the 28 died of uncomplicated hemorrhage. It seems possible, however, that the circulatory complications in six others might have been related to hemorrhage. Three patients with cerebral thrombosis, one with right femoral vein thrombosis and pulmonary embolism, and two with myocardial infarction developed circulatory complications shortly after hemorrhage. The remaining 13 had complicating disease totally unrelated to hemorrhage and of sufficient gravity to be in themselves eventually fatal. Carcinoma of the liver, carcinoma of common bile duct, cirrhosis of the liver, tuberculous pneumonia, rheumatic heart disease with congestive failure, ruptured esophageal ulcer, myelogenous leukemia, pituitary basophilism with pulmonary fat embolism, advanced arteriolar nephrosclerosis, and pyelonephritis were present in one or more of the 13 cases. Undoubtedly the acute hemorrhage from peptic ulcer added materially to the burden already imposed by serious disease, with a consequently poorer chance of survival.

Surgically Treated Cases and Analysis of Deaths

The surgically treated cases have been classified in two groups, depending upon whether or not surgery was performed as an emergency measure to stop hemorrhage. The 27 cases operated upon to stop hemorrhage comprise the group of cases in which we are most interested. There is a favorable mortality (table 4) among the surgical cases when compared to the medically treated cases which bled in the hospital, particularly among those with gastric ulcer.

Table 6 gives the types of operations carried out and the mortality of each. Again it should be stated that these operations were all carried out during the acute stage of bleeding, and many (during the early part of the study) late in the course of hemorrhage. The higher mortality with

Table VI

Type of Operation Performed during Acute Hemorrhage (27 Cases)

Type of Ulcer	Gastric Resection			Gastrotomy			Local Suture		
	Cases	Deaths	Mort.	Cases	Deaths	Mort.	Cases	Deaths	Mort.
Duodenal	11	3	27%				2	1	
Gastric	9	1	11%	1	1		1	1	
Anastomotic	2	1	50%	1	1				
Totals	22	5	23%	2	2	100%	3	2	66%

duodenal ulcer than with gastric ulcer is readily explained by the technical difficulties encountered in each type of case.

Of the three deaths following gastric resection for duodenal ulcer, one patient died of pneumonia, another of urinary shut-down, and a third was thought clinically to have died from bleeding from a second ulcer, though this was not verified by an autopsy. The one gastric ulcer death following resection occurred from bleeding from a second gastric ulcer near the cardia which was undetected at operation. The necessity of opening the stomach to identify the bleeding point was impressed upon us by this case. The one anastomotic ulcer case which died following gastric resection was due to peritonitis from leakage at the duodenal suture line. This patient was operated on late after the onset of hemorrhage, and was in a very debilitated state with poor tissue healing. The two cases which received only gastrotomy had further bleeding postoperatively from ulcers which were not seen at operation, demonstrating the difficulty which may be encountered at times in locating the bleeding point.

The two deaths following local suture of vessels occurred in persons who received late operation. One, a 62 year old diabetic, was operated on 16 days after the onset of bleeding. The second case, admitted with pneumonia, started hemorrhaging on the eighteenth hospital day. Operation was delayed until the twenty-first day, when a large gastric ulcer was found in the stomach near the cardia, with a bleeding artery in its base. Due to the very poor condition of the patient, local suture of the vessel only was carried out.

The analysis of the surgical cases with regard to the time interval between the onset of hemorrhage and operation is of interest. Five cases were operated on within 48 hours of the onset of hemorrhage, with one death (20 per cent mortality). Twenty-two cases were operated on after an interval of more than 48 hours, with eight deaths (36 per cent mortality). Finsterer,[15] Allen [16] and others have repeatedly advocated operation during the first 48 hours of hemorrhage. We feel that the decision to operate should be made as early as possible. For practical purposes we have chosen the time interval of 24 to 48 hours after entrance to the hospital. This gives time to evaluate the persistence and degree of hemorrhage and to prepare the patient for operation if bleeding does not cease.

The one death among the five cases operated on early was the man who bled from a second ulcer at the cardia mentioned above. The majority of the late cases occurred during the early part of the period studied. Many more cases are receiving early operation today in recognition of the higher mortality of late operation.

The second group of surgical cases comprises a heterogeneous group of 30 cases which had some type of procedure carried out for ulcer during their hospital stay. The majority of these people had interval operations for intractable ulcer symptoms or pyloric obstruction. However, in two

instances, perforation required plication. Both of these patients died. Six patients received vagus section, one gastroenterostomy, and the remainder gastric resection. Further analysis of this heterogeneous group does not seem warranted.

Discussion

Study of the 322 cases of the series has pointed out the necessity for detailed case analysis in any consideration of mortality from the acutely bleeding peptic ulcer. Age of the patient, duration of the ulcer, previous acute bleeding episodes, and extent of blood loss all have a bearing on mortality. Even more important are the site of the ulcer, blood loss or not after hospitalization, and the presence or absence of serious complicating diseases. Mortality rises with advancing age, is higher with gastric than with duodenal ulcer, and is increased with ulcer of short duration and with hemorrhage of a severe grade. Blood loss after hospitalization, as well as the presence of serious complicating disease, greatly increases the chance of a fatal outcome. Most of these considerations are interrelated, and some deserve special mention.

There was a rising mortality with advancing years, but gastric ulcers occurred somewhat more often in older people, bleeding in the hospital occurred more often in older people, and serious complicating disease occurred with great regularity in older people. A history lacking in ulcer symptoms previous to hemorrhage was accompanied by a higher mortality, but again this finding occurred very much more often with gastric ulcer and when there was a serious complicating disease. Fatalities occurring with a first or successive hemorrhage depended upon the site of the ulcer. Every death in the case of gastric ulcer occurred with an initial hemorrhage, whereas deaths with duodenal ulcer occurred with a first or successive hemorrhage with about equal frequency. In the series as a whole, a greater amount of blood loss was accompanied by a higher mortality. However, further study revealed the fact that this higher mortality was applicable only if there was bleeding after hospital admission.

The striking effect of blood loss under hospital conditions on the mortality rate deserves particular comment. Irrespective of age, site of ulcer, duration of ulcer and previous episodes of acute hemorrhage, the death rate is low in those patients who do not lose blood after hospital admission. This finding supports the opinion of other observers,[4, 8, 9, 13, 14] who have indicated that continued bleeding in the hospital is of great prognostic importance. The mortality of medically treated cases who did not hemorrhage after hospital admission is 1.4 per cent, irrespective of the amount of blood lost before the patient reached the hospital. There seems, therefore, no justification for surgical intervention in these patients, for it is indeed unlikely that such a figure can be bettered. Those who do continue to lose blood in the hospital, however, are poor risks and, unless there is complicating disease of such a character as absolutely to prevent operation, de-

serve the benefit of surgery. The earlier this can be accomplished, the better the chance of survival. The problem resolves itself, therefore, into the selection of those patients who, after admission, either continue to have hypotension and tachycardia despite supportive treatment, or who cease to bleed on admission but have recurrent hemorrhage some hours or days later. A third type of patient is the one who may be admitted to the hospital for an unrelated illness and subsequently has massive hemorrhage from either a duodenal or a gastric ulcer. In our experience, this type of case has had an exceedingly poor prognosis, for the patient often has complicating disease of such character as to preclude successful gastric resection. All three of these types fall into the category of hemorrhage in the hospital and should be subjected to operation, if clinically feasible, within 24 to 48 hours.

Nineteen of the 28 patients who died while being treated medically had serious complicating disease. It is difficult to state accurately what part hemorrhage and what part the complicating disease had in producing death. Undoubtedly both were important factors. In addition, three of the nine cases who died of blood loss alone were admitted moribund, and died one, four, and 14 hours after admission without any response to treatment. The occurrence of serious complicating diseases has been noted by others [5, 9, 17] but does not seem to have received deserved attention. Most certainly, in the 43 deaths of this series, such illnesses must have had an important part in producing fatalities.

What is believed to be an optimal program for the management of bleeding peptic ulcer is described below.

1. The patient is placed at complete bed rest, with adequate sedation to prevent restlessness.

2. Blood pressure and pulse rates are recorded at one half hour intervals until stabilized at a normal level, then every hour for 48 hours.

3. Blood counts, hematocrit, prothrombin time, and blood urea nitrogen are determined on admission, and the blood counts and hematocrit are repeated at least every 24 hours. The patient is typed and crossmatched, and whole blood is made available.

4. Whole blood transfusions are started at the earliest possible time. In the first 24 hours, 1,000 ml. of blood are given, and 500 ml. each successive day until the red cell count is raised above four million.

5. If the patient is not vomiting and not in shock, oral feedings of a Sippy type are begun on admission; otherwise, effort is made to provide nutrition by the parenteral route.

6. Evidences of continued bleeding manifested by sustained hypotension and tachycardia, with or without hematemesis or bloody stools, are an indication for immediate operation. Recurrent bleeding manifested by a secondary drop in blood pressure with tachycardia, with or without hematemesis or bloody stools, is also an indication for immediate operation.

7. Gastric resection with removal of the bleeding ulcer is the operation

of choice. The stomach is opened to identify definitely the bleeding point. This operation is carried out with at least 2,000 ml. of blood available. In extreme cases this is administered by the intra-arterial route (otherwise intravenously) during operation.

Summary and Conclusions

1. The records of 322 cases of bleeding peptic ulcer have been studied. Overall mortality for the series was 13.3 per cent.

2. A number of factors were related to mortality, including age of the patient, site of the ulceration, duration of the ulcer, previous acute bleeding episodes, severity of hemorrhage, bleeding after hospital admission, and serious complicating disease.

3. The most important single influence on death rate was bleeding after hospital admission. In the medically treated cases the mortality among those that did not bleed after hospital admission was 1.2 per cent for duodenal ulcer, and 3.2 per cent for gastric ulcer. The medical mortality of those that did bleed after hospital admission was 34 per cent for duodenal ulcer and 77 per cent for gastric ulcer. The surgical mortality for those patients operated on to stop hemorrhage was 31 per cent for duodenal ulcer and 27 per cent for gastric ulcer.

4. Serious complicating diseases were present in 19 of the 28 deaths of those patients treated medically, and undoubtedly were a considerable contributing influence to fatalities.

5. Patients who show evidence of continued bleeding after hospitalization should be operated on preferably during the first 24 to 48 hours. Patients who cease bleeding should be operated on when there is evidence of recurrent hemorrhage. Gastric resection is the operation of choice, and the longer it is delayed the less its chance for success.

6. An optimal program for the treatment of bleeding peptic ulcer is outlined.

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COMPARISON OF CLINICAL AND PATHOLOGIC ASPECTS OF CORONARY ARTERY DISEASE IN MEN OF VARIOUS AGE GROUPS: A STUDY OF 950 AUTOPSIED CASES FROM THE ARMED FORCES INSTITUTE OF PATHOLOGY *

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INTRODUCTION

DURING 1945 and 1946 a study was made of 866 male patients, 18 through 39 years of age, for whom the principal diagnosis was coronary artery disease. These patients included 416 who had survived typical attacks of acute myocardial infarction and whose case histories were obtained from the Veterans Administration, Washington, D. C., and 450 patients who had died while in the Army and whose autopsy protocols were in the files of the Armed Forces Institute of Pathology, Washington, D. C. The results of this study were published in the American Heart Journal [1] during 1948.

Following completion of the study of the younger age group, research was begun to determine what similarities or differences might exist in the clinical and pathologic aspects of coronary artery disease in older men as compared to those under 40 years of age. For this purpose, selection was made of 500 additional autopsy records of men 40 years of age and over. One-half of these, or 250, were men 40 through 49 years of age; the other 250, men 50 years of age and older. In order to obtain more definite comparison of age groups, some of the original data on men under 40 years of age were divided into two categories, one relating to men aged 18 through 29 years, and the other to those 30 through 39 years. Thus the present report is based on the records of 950 men dying of coronary artery disease which were in the files of the Armed Forces Institute of Pathology. Six hundred thirty-five of the men served in the Army during World War II. Most of the others were soldiers who had died before that time, and a few were civilians connected with the armed forces.

The 950 cases do not represent the total deaths from coronary artery disease recorded at the Armed Forces Institute of Pathology as of May 1, 1947, the date when the series in this report was concluded. Many protocols were discarded because of insufficient clinical or pathologic data. The pathologic material was inadequate for microscopic review in 266 of the

* Presented in preliminary form at the Twenty-eighth Annual Session of the American College of Physicians, Chicago, Illinois, May 2, 1947.

cases selected, but they were included because the descriptions by the prosectors were sufficiently complete to establish the diagnosis beyond doubt. The cases studied, with few exceptions, were those in which coronary artery disease was obviously the cause of death.

The arbitrary basis of selection of cases in each age group, as well as the fact that most of the material in the Armed Forces Institute of Pathology is obtained from military sources, precludes comparisons of the prevalence of coronary artery disease in this series with that in the total male population of the United States or with the strength of the Army. Furthermore, comparison of the incidence of clinical and pathologic features with those of the civilian population at large must be made with consideration for the fact that men in the Army are often retired from the service if they are known to have coronary artery disease. Such consideration is important, for instance, in the length of time before death that symptoms of heart disease were noted. Also, some men, especially officers, may not divulge their illnesses to medical officers for fear of lengthy hospitalization and/or retirement.

That the 635 fatalities from coronary artery disease among World War II soldiers in this series do not represent, either numerically or percentagewise, the total picture of its incidence among military personnel is shown by the fact that as of June 30, 1948, 6,075 World War II veterans were receiving service-connected disability pension awards principally because of coronary artery disease. Coronary occlusion, thrombosis or sclerosis, and angina pectoris were the major disabilities specified for 5,345 of these men, and myocardial infarction was listed for 730. No age breakdown is available on these men, but of 2,684 World War II veterans who were receiving awards for these defects on October 15, 1945, 1,322, or 49 per cent, were in the age group 16 through 39 years, 1,104, or 41 per cent, were 40 through 49 years of age; and 258, or 10 per cent, were 50 years of age and over.

Although the material on men aged 18 through 39 years in this series is the same as that used in the report published in the American Heart Journal,[1] additional data which had been received and minor changes for comparability necessitated a revision of some figures which appeared in the earlier report. However, none of the changes was of sufficient magnitude to affect the data seriously.

Few references are made to medical literature, since very little has been written on the subject of this report.

Etiologic Considerations

Age. As table 1 shows, 47 per cent of the men were under 40 years of age and approximately 12 per cent of the total were under 30. The average age was 43.2 years, and 68 per cent of the men were between 30.6 and 55.8 years of age. The youngest was 18 years of age and the oldest, a Negro, was 86.

TABLE I

Age Distribution of Men with Coronary Artery Disease by Five-year Age Groups

Age Group	Per Cent		Number	
18–24	4.	12.	42	120
25–29	8.		78	
30–34	15.	35.	142	329
35–39	20.		187	
40–44	14.	26.	135	250
45–49	12.		115	
50–54	10.		92	
55–59	5.		48	
60–64	5.		46	
65–69	3.	27.	30	250
70–74	2.		17	
75–79	1.		11	
80–84	1.		5	
85–89			1	
Total	100.[1]		.950[2]	

[1] Based on 949, the men with age known.
[2] Total includes 1 patient whose age was not definitely stated but was known to be under 40 years.

Race. Thirty-nine or 4.1 per cent of the 950 patients were Negroes (table 2). Their average age (arithmetic mean) was 38.8 years; 51 per cent were 30 through 39 years of age.

Approximately 12 to 15 per cent of the material in the files of the Armed Forces Institute of Pathology consists of surgical and autopsied cases contributed by civilian physicians because the cases are of interest for teaching and research purposes. Since this material is highly selective, no conjecture as to relative frequency of deaths in the two races can be made by use of the entire series. However, such a comparison is possible if the data are re-

TABLE II

Age Distribution of White and Negro Men with Coronary Artery Disease by Ten-year Age Groups

Age Group	Per Cent		Number	
	White[1]	Negro	White[1]	Negro
18–29	12.	15.	114	6
30–39	34.	51.	309	20
40–49	27.	18.	243	7
50–59	15.	5.	138	2
60–69	8.	8.	73	3
70–79	3.	—	28	0
80–89	1.	3.	5	1
Total	100.	100.	910	39

[1] Includes all races other than Negro, of which there were 4 non-white. The age of 1 white man was not stated but was known to be under 40 years.

stricted to World War II soldiers in the series. It is known that Negro males comprised approximately 10 per cent of the World War II Army, as they do of the total male population 18 years of age and over.

Only 24 (3.8 per cent) of the 635 men in the series who were soldiers on active duty during World War II were Negroes, a much lower percentage than the 10 per cent of Negroes in the total Army population during the period. The probability of receiving autopsy material on soldiers of either race who died of coronary artery disease was equal, and for this reason it appears likely that the disease actually occurs less frequently in Negroes than in white men. In the previous article [1] it was indicated that coronary artery disease appears to be about two-thirds as common in Negroes aged 18 to 39 years inclusive as in Caucasians of the same group. For this age group the incidence in the two races could be fairly accurately determined.

TABLE III

Length of Army Service of World War II Soldiers with Coronary Artery Disease

Length of Army Service	Per Cent in Age Group			
	18–29	30–39	40–49	50 and Over
0–6 months	19.	30.	20.	6.
7–12 months	17.	21.	20.	2.
13 months to 3 years	54.	34.	20.	9.
3 to 6 years	8.	7.	5.	—
6 to 10 years	1.	1.	7.	4.
10 years and over	1.	7.	28.	79.
Total	100.	100.	100.	100.
Total with length of service known	69	214	56	47
Total World War II soldiers	111	302	131	91

Length of Army Service. That 135 (48 per cent) of World War II soldiers under 40 years of age whose length of Army service was known died within their first year of military service indicates that they may have had coronary artery disease at the time of induction or enlistment. Table 3, showing the length of Army service of the 386 men who died while on active duty during World War II and for whom the length of service was known, includes 78 who had been in the Army prior to World War II.

It was considered that a sudden change from civilian life to the rigors of basic training and the adjustment to army life under conditions of war or threat of war might have precipitated the fatal "attacks" of coronary artery disease. On this premise, the average length of army service of the 308 men who entered the Army after July 1, 1940,* for whom length of service was

* July, 1940, marked the beginning of the rapid growth in size of the Army, with enlistments increasing as Congress considered passage of the peacetime Selective Training and Service Act of 1940.

known was computed for each age group. The average length of service of these men was approximately 17 months, as compared with two and one-half years for all inductees and enlistees during World War II.*

The average length of service was 20 months in the age group 18 through 29, 15.6 months among men 30 through 39, and 15.9 months among those 40 years of age and over. Although this difference in the men under 30 and those 30 and over is slight, a tendency toward greater ability of men under 30 years of age to withstand the stress of basic training is indicated by their longer average time in military service; 63 per cent of these men lived longer than one year after entry into service, as compared to 45 per cent of the men aged 30 through 39, and 41 per cent of those 40 years of age and over, among whom the differences in survival of one year or less and 13 months to six years (the World War II period) were not statistically significant.

TABLE IV

Height-Weight Factor at Time of Death of Men with Coronary Artery Disease

Height-Weight Factor	Per Cent in Age Group			
	18–29	30–39	40–49	50 and Over
Normal or below	40.	34.	43.	45.
Moderately overweight	45.	43.	28.	22.
Greatly overweight	15.	23.	29.	33.
Total	100.	100.	100.	100.
Total men with data	94	262	196	242
Per cent of men in group	78.	79.	78.	97.

No definite conclusions can be drawn as to the rôle of army life in precipitating fatal "attacks" of coronary artery disease, since these men might have died at the same ages if they had remained in civilian life. However, the generally shorter length of service as compared with that of the average from the World War II Army suggests that these men were not in condition to withstand the stress of army life, a fact which in many cases could not have been detected even with more elaborate examinations than those made at time of entrance into military service.

Height-Weight Relationship. The heights and weights of 794 men at the time of death were recorded in the autopsy protocols. Although these were not entirely accurate, allowance for inaccuracies was made in the designation of "overweight" from the standard table of heights and weights for men by individual year of age which was used as a criterion.[2]

Data obtained by computation of the height-weight relationship of each man were grouped in accordance with definitions previously used in the

* Average length of service for World War II soldiers was two and one-half years, according to figures supplied by the Office of The Adjutant General, Department of the Army.

study of men 18 through 39 years of age,[1] that is, the lowest 62.5 per cent of the standard distribution was considered of normal weight or below; the next 25 per cent, moderately overweight; and the top 12.5 per cent, greatly overweight. On the basis of these definitions, more than one-half of the men in each group in the present study were considered overweight, either moderately or greatly, although in general the percentages decreased slightly with increasing age (table 4). There was, however, a decided shift toward "great overweight" among men 50 years of age and over. Underweight men were not considered separately, since a comparison of the underweight men below age 40 with a group of Army inductees of the same ages indicated that it was not a significant etiologic factor.

The previous report on men aged 18 to 39 years [1] revealed that "the men, on the whole, gained weight during their Army careers; and, although it is true that most of those who died of coronary artery disease were overweight in comparison with all inductees, they were no heavier than others who had been in army service for a time but who did not have coronary artery disease." For this age group, the size of the control group was adequate for comparison, whereas for the other age groups, adequate controls could not be obtained.

Hypertension. Another possible etiologic factor which could not be thoroughly analyzed for lack of complete data was the existence of hypertension. Blood pressure measurements, particularly among the older men, were made at varying stages of hospitalization, some while the men were definitely in a state of shock, so that comparison is difficult. However, men with histories of hypertension and those with persistent blood pressure measurements of 150 mm. Hg systolic and 90 mm. diastolic and over were counted as definitely hypertensive, and these numbered 18 among men under 40 years of age, 32 of the men 40 through 49, and 58 of those 50 years of age and older (see table 9). The corresponding percentages were 4, 13, and 23; thus, the percentage of men in the oldest group who had known hypertension was relatively six times as great as in the youngest group. Induction and enlistment records were available for the men under 40, and blood pressures of this group were thoroughly discussed in the previous article.[1]

Precipitating Factors

Except for the length of service of World War II soldiers already discussed, the only factors which might have precipitated the acute "attacks" of coronary insufficiency, coronary artery thrombosis or myocardial infarction, and which could be investigated for all age groups, were the types of activity in which the men were engaged at the time of onset of the terminal illness. The influence of the type of activity is presented here, with the conclusion that, while activity which may be described as strenuous did not appear to be a precipitating factor in the fatal illness of the men aged 40 and over, it was apparent in men under 40.

Activity When Stricken. In order to evaluate the possible influence of the type of activity in which the men were engaged at the onset of the terminal "attack" of coronary insufficiency or myocardial infarction, a tabulation was made of the activities in which 611 were engaged at the time of their "attacks." For this purpose, the men were divided as to type of activity into four groups: those in bed at the time of the acute "attack," those engaged in mild activities such as sitting still and eating, those moderately active, that is, walking, rolling pads, or in latrine, and those engaged in more strenuous activities, such as running, marching, drilling, calisthenics and athletics.

As table 5 shows, the percentages of men whose activity was less than strenuous at the time of the acute "attack" which marked the onset of the terminal illness increased with advancing age. A high percentage of older men stricken while in bed is to be expected, since they are in general less

TABLE V

Activity at Onset of Acute "Attack" in Men with Coronary Artery Disease

Activity at Onset	Per Cent in Age Group			
	18–29	30–39	40–49	50 and Over
In bed	20.	23.	25.	33.
Mild	25. } 48.	31. } 50.	43. } 62.	22. } 52.
Moderate	23. }	19. }	19. }	30. }
Strenuous	32.	27.	13.	15.
Total	100.	100.	100.	100.
Total men with activity known	88	238	150	135

likely than younger men to be engaged in strenuous physical activities. However, if the 24-hour day be arbitrarily divided into an estimated 33 per cent of the time spent in bed, 54 to 56 per cent in mild or moderate activities, and 11 to 13 per cent in strenuous activities, it is apparent that in the two youngest age groups strenuous activity was more often associated with the onset of the acute "attack" then in the older age groups.

A comparison was made on the basis of the presence or absence of coronary thrombosis and ages of thrombi in relation to the activity at the onset of the acute terminal "attack" (table 6). (It should be noted that the percentages in this table are based on the total number of men in each age group with known activity.)

This table indicates that in both the "in bed" and the "mild or moderate" activity categories, the percentages of men with old, or recent and old, thrombi increased with advancing age. A slight increase was also noted among men engaged in strenuous activity, but the number of older men in this category was too small to be conclusive.

In evaluating these figures, the proportion of time spent in the various activities must be considered, and it must be remembered that a thrombus may have started to form hours before the actual "attack." Therefore, no clear connection could be seen between the presence or absence of a thrombus and the activity of the men at onset of the "attack," although it appeared in the previous study of men under 40 that strenuous activity might be a precipitating factor.

TABLE VI

Ages of Coronary Thrombi in Relation to Activity at Onset of "Acute Attack" in Men with Coronary Artery Disease

Ages of Coronary Thrombi	Activity at Onset in Age Group								
	In Bed			Mild or Moderate Activity			Strenuous Activity		
	18–39[1]	40–49[2]	50 and Over[3]	18–39[4]	40–49[5]	50 and Over[6]	18–39[7]	40–49[8]	50 and Over
	Number								
Recent and/or organizing	24	10	21	74	45	14	38	5	5
Old alone or with recent	2	2	11	9	10	8	6	1	1
Total with data	26	12	32	83	55	22	44	6	6
No thrombi	42	25	51	72	34	45	45	14	13
	Per Cent								
Recent and/or organizing	92.	83.	66.	89.	82.	64.	86.	83.	83.
Old alone or with recent	8.	17.	34.	11.	18.	36.	14.	17.	17.
Total with thrombi	100.	100.	100.	100.	100.	100.	100.	100.	100.

[1] 1 case with recent and organizing thrombi.
[2] 2 cases with recent and organizing and 1 case with old and recent thrombi.
[3] 4 cases with old and recent thrombi.
[4] 6 cases with recent and organizing and 4 cases with old and recent thrombi.
[5] 1 case with recent and organizing and 4 cases with old and recent thrombi.
[6] 3 cases with old and recent thrombi.
[7] 2 cases with recent and organizing thrombi.
[8] 1 case with old and recent thrombi.

When the presence or absence of myocardial infarcts among men 18 through 39 years of age, as compared to those among men 40 years and over, was considered in relation to the type of activity, no significant relationship was found.

PREVIOUS CARDIAC HISTORY

Previous Cardiac History. The number of men in the entire series who were able to give a history or for whom others were able to supply this information was 591.

Table 7 shows the distribution in each of the three age groups of men with no previous cardiac history, of those with only "premonitory" * symptoms within three weeks of the terminal illness, and of those with definite or strongly probable cardiac manifestations more than three weeks before the fatal illness. Some of those in the last group also had symptoms (premonitory) within three weeks of the onset of the terminal "attack."

On the basis of these data, the percentage of men who had survived definite or probable cardiac "attacks" three weeks or more before the onset of the terminal illness increased significantly at or after age 40. "Premonitory" symptoms also occurred more often from age 40 on. Therefore, men 18 through 39 years of age appeared much more likely to die during the initial "attack" and without prior manifestations of cardiac disease than were those 40 years of age or over. Only 9 per cent of the men 40 and over for whom information was available reported no definite, probable or "premonitory" symptoms of cardiac difficulty prior to the terminal illness, as compared to 48 per cent of those under 40 years of age.

TABLE VII

Previous Cardiac History of Men with Coronary Artery Disease

Previous Cardiac History	Per Cent in Age Group			Number in Age Group		
	18–39	40–49	50 and Over	18–39	40–49	50 and Over
No previous history	48.	9.	10.	105	14	20
"Premonitory" symptoms within 3 weeks[1]	9.	29.	26.	20	48	55
Definite or probable 3 weeks or over	43.	62.	64.	93	102	134
Total with adequate history	100.	100.	100.	218	164	209
Per cent of men in group	48.	66.	84.			

[1] This category does not include men with definite or probable clinical manifestations 3 weeks or more before the onset of the terminal "attack" who also had symptoms within 3 weeks of the terminal "attack."

Relation of Previous Cardiac History to Myocardial Lesions. Data were available in 591 cases both as to previous cardiac history and as to myocardial infarcts described grossly or microscopically at autopsy. The numbers and percentages of men with and without infarction in relation to the previous history are shown in table 8.

The majority of the younger men (under 40 years of age) had no myocardial infarcts; this was true even in the group with a definite history of cardiac disease more than three weeks prior to the terminal illness.

Among men under 40 years of age and those 40 and over who reported no previous cardiac history there was no significant difference in the per-

* The designation of "premonitory" symptoms within three weeks was made on a purely arbitrary basis.

centages with infarction (21 and 35 per cent, respectively). When there was a history, however, more than twice as many men 40 years of age or over had myocardial infarcts as did men under 40 (72 per cent of the older men as compared to 33 per cent of the younger).

The incidence of myocardial fibrosis found on histologic examination (see table 35) was investigated in relation to previous cardiac history, and an increasing tendency toward fibrosis as age increased was observed. Increasing coexistence of myocardial fibrosis and infarction also became evident as age increased, particularly in men who gave a history of cardiac disease.

TABLE VIII

Previous Cardiac History in Relation to Myocardial Infarcts Among Men with Coronary Artery Disease

Previous Cardiac History	Myocardial Infarcts in Age Group					
	18–39			40 and Over		
	No Infarcts	Infarcts[1]	Total	No Infarcts	Infarcts[1]	Total
	Number					
No history[2]	83	22	105	22	12	34
History[3]	76	37	113	96	243	339
	Per Cent					
No history[2]	79.	21.	100.	65.	35.	100.
History[3]	67.	33.	100.	28.	72.	100.

[1] Includes myocardial infarcts not described grossly but noted on microscopic examination.
[2] Definite statement of no history.
[3] Includes definite history, possible history and "premonitory" symptoms within 3 weeks of onset of terminal illness.

Specific Manifestations of Coronary Artery Disease. The specific manifestations which had preceded the terminal illness and which might sooner have suggested disease of the coronary arteries were investigated, with the results shown in table 9.

Previous attacks of coronary insufficiency * had occurred in 197, or one-third of the 591 men with definite or probable history of cardiac difficulty, but there was no significant difference in the occurrence in men under 40 and in those 40 years of age and over. Men aged 40 and over were more likely than the younger men, however, to have dyspnea, congestive failure, and previous attacks diagnosed clinically as myocardial infarction.

* Coronary insufficiency as used here denotes isolated attacks of thoracic pain not dependent on exertion and often accompanied by sweating, weakness and other signs of shock in some degree, but not followed by electrocardiographic or other manifestations of myocardial infarction. Such attacks have often been referred to in the literature simply as angina pectoris.

The same was true with respect to occurrence of previous angina of effort in men under 40 as compared to those 40 years of age and over.

Evidence of hypertension as shown in this table was discussed in the section "Etiologic Considerations."

It should be borne in mind that the tests of statistical significance with respect to all these previous cardiac conditions are based on the assumption that these conditions had not been present if they were not mentioned in the clinical histories contained in the autopsy protocols. It is possible that in some cases conditions which may have preceded the terminal illness were never recognized or clinically diagnosed.

TABLE IX

Previous Manifestations of Cardiovascular Disease in Men with Coronary Artery Disease

Previous Cardiac Conditions	Age Group					
	Per Cent			Number		
	18–39	40–49	50 and Over	18–39	40–49	50 and Over
Coronary insufficiency	35.	30.	35.	76	48	73
Angina of effort	7.	10.	7.	15	17	15
Dyspnea	5.	7.	12.	11	11	26
Congestive failure	2.	13.	15.	5	22	31
Previous clinical infarction	2.	16.	12.	5	26	25
Known hypertension[1]	4.	13.	23.	18	32	58
Total men with data				218	164	209

[1] Systolic pressure of 150 mm. Hg or over and diastolic pressure of 90 mm. Hg or over. Percentages were based on the total men in the series, i.e., 18–39, 450; 40–49, 250; 50 and over, 250.

Duration of Previous Cardiac Conditions. Accuracy of any statement of the length of time during which there had been previous attacks of coronary insufficiency, angina of effort, and dyspnea alone or in conjunction with fully developed congestive failure before the onset of the terminal "coronary attacks," is largely dependent upon the reliability of the patient's memory.

When men under 40 with definite duration known were compared to those 40 and over, it was found that within six months of the fatal illness coronary insufficiency occurred significantly more often in the younger than in the older men. There was no difference between the age groups with respect to duration of angina of effort. The data on dyspnea and congestive failure were too few to permit comparison.

Myocardial Infarcts in Relation to Previous Manifestations of Cardiac Disease. Myocardial infarcts were observed grossly in 34, 65 and 64 per cent, respectively, of the men aged 18 through 39, 40 through 49, and 50 and over with a history of coronary insufficiency. A small percentage in

each age group had infarcts of undesignated age; in those with age of infarcts known, recent or organizing infarcts were more frequently found in the age group 18 through 39, whereas old, or both recent and old combined, occurred more frequently among men in each of the two older groups.

Angina of effort appeared to be associated significantly with myocardial infarction only in men aged 40 and over.

The incidence of myocardial infarcts with previous congestive failure decreased with age, which was surprising. However, there were only five men under 40 who had had congestive failure. Of the 58 men who had had congestive failure, 32 had infarcts; old infarcts or a combination of old and recent predominated over recent.

TABLE X

Duration of Previous Manifestations of Cardiac Disease in Men with Coronary Artery Disease

Duration	Number in Age Group											
	Coronary Insufficiency			Angina of Effort			Dyspnea			Congestive Failure		
	18–39	40–49	50 and Over	18–39	40–49	50 and Over	18–39	40–49	50 and Over	18–39	40–49	50 and Over
Less than 3 weeks	15	3	38	2	1	1	3	2	2	3	3	7
3 weeks to 1 month	—	—	—	—	—	—	—	—	—	—	—	—
1–3 months	25	7	9	4	4	2	1	2	3	1	5	5
4–6 months	5	2	2	—	—	1	1	2	3	—	2	5
7 months—1 year	9	15	6	5	4	2	1	1	7	—	6	2
2–4 years	1	11	7	—	5	5	—	3	6	—	2	7
5–7 years	—	1	3	—	1	1	—	—	2	—	1	2
8–10 years	—	—	3	—	1	1	—	—	1	—	—	—
11 years and over	—	1	2	1	—	1	1	—	1	—	—	—
"Several months or years"	21	6	3	3	—	1	2	—	1	1	1	2
Duration not known	—	2	—	—	1	—	2	1	—	—	2	1
Total with data	76	48	73	15	17	15	11	11	26	5	22	31

Among the 48 men with dyspnea unassociated with full congestive failure, a higher percentage of the men 40 through 49 years of age had myocardial infarcts than was true of the other two age groups. In the younger (18 through 39) age group, only recent infarcts were found, and in the other two there was no difference between the occurrence of all recent and all old infarcts.

Known hypertension, which occurred more frequently in conjunction with dyspnea alone than with fully developed congestive failure, contrary to expectation, did not appear to be an important factor in relation to congestive failure. Hypertension was not present in the men 18 through 39 with congestive failure, was present in only one of 22 men aged 40 through 49, and in four of 31 who were 50 years old or over who had congestive

failure. It was found with dyspnea alone in eight of 26 men in the 50 and over age group, but was not recorded for men under 50.

Duration of Terminal Illness

The duration of the terminal illness of men in this series is based on the 891 for whom a definite duration was reported, although it was probable that the length of terminal illness was less than 24 hours for the 59 men who were found dead or dying and for whom no information was available. Table 11 shows clearly the tendency toward longer survival following the acute "coronary attacks" which initiated the terminal illness as age increased, the percentage rise being from 15 with a duration of more than 24 hours in the youngest group to 50 in the oldest.

Table XI

Duration of Terminal Illness Among Men with Coronary Artery Disease

Duration of Terminal Illness	Per Cent in Age Group			
	18–29	30–39	40–49	50 and Over
Instant death[1]	52. } 85.	43. } 80.	40. } 57.	39. } 45.
Less than 1 day	33. }	37. }	17. }	6. }
1–7 days	8. } 15.	8. } 16.	12. } 35.	16. } 50.
1 week to 3 months	7. }	8. }	23. }	34. }
3 months or over	—	4.	8.	5.
Total	100.	100.	100.	100.
Total with duration known	111	291	241	248

[1] Includes instant death or death in less than 1 hour.

Differences in survival in the various age groups are of interest. Men under 40 years of age were more likely to die within 24 hours of the "acute attacks" than to survive one day or longer. In the age group 40 through 49 there was no significant difference in the number who died within 24 hours and those who lived one day or longer, but significantly more men 50 years of age or over lived one day or longer. Generally, it may be said that the men 40 years old and over tended to have a longer terminal illness than did those under 40. Table 12 indicates that the trend was the same among men who had had previous manifestations of cardiac disease more than three weeks before the fatal "attack."

Among the 891 men duration of whose terminal illness was known, 58 per cent of 353 men with gross myocardial infarcts survived one day or longer, as compared to 26 per cent of 538 men without such infarcts. Men with any type of occlusion of the coronary arteries and myocardial infarcts tended to survive one day or longer. In contrast, men with occlusion but no myocardial infarcts were more likely to die within one day than to survive

TABLE XII

Duration of Terminal Illness in Relation to Previous Cardiac History Among Men with Coronary Artery Disease

Previous Cardiac History	Duration in Age Group					
	Less Than 24 Hours			24 Hours or More		
	18–39	40–49	50 and Over	18–39	40–49	50 and Over
	Number					
No previous history	19	10	17	23	3	3
"Premonitory," within 3 weeks[1]	4	20	23	16	27	32
Definite, over 3 weeks	38	28	28	23	59	93
Possible or probable	12	5	5	10	7	6
Total	73	63	73	72	96	134
	Per Cent					
No previous history	26.	16.	23.	32.	3.	2.
"Premonitory," within 3 weeks[1]	6.	32.	32.	22.	28.	24.
Definite, over 3 weeks	52.	44.	38.	32.	62.	69.
Possible or probable	16.	8.	7.	14.	7.	5.
Total	100.	100.	100.	100.	100.	100.

[1] This category does not include men with definite or probable clinical manifestations 3 weeks or more before the onset of the terminal "attack" who also had symptoms within 3 weeks of the terminal "attack."

for a longer period. When there was no occlusion but only "simple narrowing" of the coronary arteries, the presence or absence of infarcts made no significant difference with respect to survival.

The tendency toward early death without infarction was found only in men under 40 years of age, except when both thrombotic and sclerotic occlusion occurred in combination, in which case the older men also tended to die within 24 hours of the onset of terminal illness. The longer survival period of men with infarcts was found significantly often only in men aged 40 and over.

As would be expected, the presence of mural thrombi was significantly related to a terminal illness lasting 24 hours or longer, since infarction appeared to be the main cause of mural thrombus formation in these men. Only 25, or 6 per cent, of the 392 men who lived less than one day had mural thrombi, as compared to 118, or 41 per cent, of the 287 who lived 24 hours or longer.

Two-thirds of the men for whom the entire duration from the onset of signs or symptoms of cardiac disease to the time of death was known reported symptoms of less than one year's duration; 86 per cent of these men

TABLE XIII

Duration of Illness from Onset of Symptoms of Coronary Artery Disease to Death

Duration of Illness	Age Group					
	Per Cent			Number		
	18–39	40–49	50 and Over	18–39	40–49	50 and Over
Unknown	75.	49.	25.	336	122	63
None (instant, seconds or minutes)	4.	4.	8.	16	9	19
Less than 1 day	1.	5.	5.	5	11	12
1–3 days	2.	4.	3.	9	9	7
4–6 days	2.	1.	1.	8	2	3
1–2 weeks	3.	5.	8.	12	13	21
3 weeks to 1 month	1.	1.	1.	6	3	2
1–3 months	6.	8.	9.	26	21	22
4–7 months	2.	3.	4.	11	8	9
8–11 months	1.	4.	2.	5	9	5
1–2 years	2.	13.	12.	11	33	30
3–4 years	1.	1.	10.	5	3	26
5–6 years	—	2.	4.	—	4	11
7–8 years	—	—	4.	—	—	9
9–10 years	—	[1]	2.	—	1	5
11–12 years	—	[1]	[1]	—	1	1
13 years and over[2]	—	[1]	1.	—	1	2
Years, not specified as to number	—	—	1.	—	—	3
Total	100.	100.	100.	450	250	250

[1] Less than one-half of 1 per cent.

[2] Includes 1 case in the 40–49 age group with duration of 17 years and 2 cases in the 50 and over age group with durations of 20 and 24 years.

under 40 years of age died within a year of first symptoms, as compared to 59 per cent of those aged 40 and over (table 13).

Since a fairly high percentage of the older men reported symptoms of several years' duration, their ages at onset were computed to determine whether any had noticed these symptoms before the age of 40. Only 11 of the 315 might have been under 40 years of age at the time of onset; however, 16 of the men aged 50 and over reported symptoms which might have begun before age 50.

SYMPTOMS AND SIGNS OF THE ACUTE "ATTACK"

Symptoms and Signs of the Terminal Illness. A summary of the symptoms which characterized the onset and course of the terminal illness is shown in table 14.

Pain, which was the most commonly reported symptom, was almost universally present in the age group under 30, occurring in 98 per cent of

these men; but it decreased with advancing age, occurring in 84 per cent of the oldest age group. It should be noted that the percentages of men with pain were based on the number who survived long enough and were not too ill to question, whereas the symptoms and signs other than pain were based on these and an additional number of men who were observed during the course of the terminal illness, even though some were too ill to question. It is possible that pain marked the onset of the terminal illness in many men for whom information was not available.

The symptoms and signs included in the "shock" category were simple statements of "shock," weakness or fatigue, collapse, sweating, cyanosis, weak and/or rapid pulse, pallor, tachycardia, palpitation, and a sensation of abnormal bodily heat. One or more of these manifestations were recorded for 54 per cent of the men from whom such information was available.

A comparison of the incidence of specific manifestations of shock in men under 40 and those of 40 and over indicated that, although there was no significant difference in the occurrence of total manifestations of shock in the two age groups, "collapse" occurred significantly more often in men under 40 than in those aged 40 or over. In contrast, cyanosis occurred significantly more often in the older men.

Other specific signs and symptoms which occurred more often in men under 40 than in those aged 40 years or over were nausea and/or vomiting, other gastrointestinal disorders, convulsions, syncope, and other nervous

TABLE XIV

Summary of Symptoms and Signs of Coronary Artery Disease from Initial "Attack" of Terminal Illness to Death

Signs and Symptoms	Per Cent in Age Group				Number in Age Group			
	18–29	30–39	40–49	50 and Over	18–29	30–39	40–49	50 and Over
Pain[1]	98.	97.	92.	84.	61	175	160	144
Manifestations of shock	60.	51.	45.	63.	59	129	91	133
Respiratory symptoms	26.	37.	48.	63.	26	94	95	132
Gastrointestinal disorders	34.	25.	17.	19.	34	64	34	41
Central nervous system disorders	19.	30.	21.	18.	19	77	42	39
Congestive failure	3.	6.	23.	34.	3	14	46	72
Embolization[2]	1.	2.	2.	4.	1	4	3	8
Other symptoms[3]	6.	5.	4.	3.	6	13	7	6
Tenderness in right upper quadrant of abdomen, enlarged liver	—	2.	3.	17.	—	5	5	35
Total men with data					99	253	199	211
Per cent of men with data	82.	77.	80.	84.				

Note: Each symptom was counted once for each patient regardless of the number of times it occurred during the course of terminal illness.

[1] Since some of the men died too suddenly or were too ill to question, the pain percentages were based on the following totals: 18–29, 62; 30–39, 180; 40–49, 173; 50 and over, 171.

[2] Diagnosed clinically.

[3] Includes aching in joints, anorexia, thirst, numbness of left upper extremity, chills, etc.

manifestations, such as restlessness, nervousness, groaning and mental dullness. Men aged 40 and over appeared more likely than those under 40 to have one or more of the following symptoms: pulmonary congestion, congestive failure, embolization, and tenderness of the abdomen, due, no doubt, to acute congestion of the liver.

In summary, the terminal illness of men under 40 years of age was characterized by the more violent symptoms, such as pain, collapse, gastrointestinal disorders, and certain nervous manifestations. The types of activity in which the men were engaged at the time of the initial "attack" of terminal illness were not considered in relation to the signs and symptoms, but it is possible that the strenuous activity in which the high percentage of young men were engaged had some influence on the severity of their symptoms.

TABLE XV

Location of Pain at Onset of Acute "Attack" in Men with Coronary Artery Disease

Location	Per Cent in Age Group			
	18–29	30–39	40–49	50 and Over
Thoracic, anterior	80.	78.	84.	83.
Location not stated	42.	27.	4.	2.
Precordial	18.	27.	41.	32.
Substernal	20.	24.	39.	49.
Thoracic, posterior	2.	4.	—	1.
Abdominal	25.	19.	18.	15.
Left shoulder and arm	12.	8.	3.	2.
Both shoulders and arms	—	6.	1.	2.
Total with location known	60	167	155	131
Per cent of men in group	50.	51.	62.	52.

Note: Locations given are those in which the pain first appeared.

Pain as a Symptom During the Terminal Illness. Anterior thoracic pain was present initially in 78 to 84 per cent of the patients for whom the location of pain was known (table 15). The division of anterior thoracic pain into precordial and substernal is admittedly inaccurate, and the percentage of men in the 18 through 29 and 30 through 39 year age groups for whom the location of the anterior thoracic pain was not definitely stated was high; therefore, the apparent tendency toward increase in substernal pain as age advanced cannot well be measured statistically.

Posterior thoracic pain was found in 1 to 4 per cent of the patients, but showed no consistent pattern in the various age groups. Abdominal pain decreased slightly but not significantly with advancing age, while pain in the left shoulder and arm also became a less important symptom in the older men than in the men under 30 years of age.

A fairly high percentage of men in each age group did not report radiation of the initial pain. On the assumption that it did not radiate, the rela-

tion of the initial location of the pain to the area of radiation was evaluated for the remaining men (table 16). Anterior thoracic pain, which radiated to the left arm in two-thirds of the 102 patients under 50 years of age, was more likely to affect both arms in men 50 years of age and over (30 of 58 patients).

Characteristics of Men Without Pain. A study was made of various characteristics of the 46 men in the series who were definitely reported as not having pain at the time of the acute "attack." Six of these were under 40 years of age, and the others were 40 years of age or older. They were, on the average, 55 years of age, considerably older than the average of men in the entire series. The total duration of illness from onset of symptoms to death was less than one year for 16 of 39 men with stated duration. For 22 of the remaining 23, all of whom were aged 40 and over, the duration ranged from one to nine years. One man in the 50 and over age group reported

TABLE XVI

Radiation of Pain at Onset of Acute "Attack" in Men with Coronary Artery Disease

Area of Radiation	Per Cent in Age Group			
	18–29	30–39	40–49	50 and Over
Left arm and/or hand	63.	49.	60.	31.
Both arms, arms and back	37.	38.	30.	52.
Right arm	—	3.	3.	3.
Chest, precordium	—	7.	4.	5.
Back, interscapular area	—	3.	3.	9.
Total	100.	100.	100.	100.
Total with radiation known	8	29	76	58
Per cent of men in group	7.	9.	30.	23.

symptoms of 20 years' duration. When the prevalence of symptoms other than pain was compared for the group known to be without pain and those who definitely experienced pain, it appeared that a significantly higher percentage of manifestations of shock occurred in men who experienced pain than in men who did not. In contrast, congestive failure occurred significantly often in men without pain, as did tenderness in the right upper quadrant of the abdomen. The 10 men with the latter symptom were all aged 50 and over.

Comparison of manifestations of shock and respiratory symptoms in men under 40 and those 40 years of age or over who had no pain showed no significant differences in these two age groups with respect to symptoms of either type.

There was no significant difference in the 46 men who did not experience pain and the remainder of the men in the series with respect to the presence or absence of infarcts or to the ages of the infarcts. Six had old infarcts;

five, recent infarcts; five, both old and recent ones, and two had infarcts of unstated age.

The percentage of coronary thrombi was significantly higher in the men without pain than in the remainder of the patients. Thirty, or 65 per cent, of the men without pain had coronary thrombi, as compared to 432, or 47 per cent, of the 904 who had pain or for whom the occurrence of pain could not be determined. There was no apparent relationship between the ages of the coronary thrombi and the presence or absence of pain. Only three (7 per cent) of the men without pain had thrombotic occlusion alone, as compared to 24 per cent of the remaining men in the series. The percentages with both thrombotic and sclerotic occlusion and with sclerotic occlusion alone were approximately the same in men with and without pain.

TABLE XVII

Cardiac Signs in Men with Coronary Artery Disease

Cardiac Signs	Per Cent in Age Group			Number in Age Group		
	18–39[1]	40–49	50 and Over	18–39	40–49	50 and Over
Abnormal heart sounds						
Distant, poor quality	24.	29.	38.	7	26	48
Roughening of first heart sound, split apical first sound	3.	—	2.	1	—	3
Tic-tac rhythm	3.	2.	2.	1	2	2
Gallop rhythm	17.	12.	6.	5	11	7
Tachycardia[2]	17.	21.	29.	5	19	36
Extrasystoles, irregular pulse, arrhythmia	17.	15.	26.	5	13	33
Murmurs						
Systolic	21.	18.	15.	6	16	19
Systolic and diastolic at apex	—	3.	6.	—	3	8
Diastolic, aorta area	3.[1]	—	2.	1[1]	—	2
Pericardial friction rub	3.	8.	9.	1	7	11
Cardiac enlargement	21.	27.	44.	6	24	56
Total men with data				29	89	126

[1] Syphilitic aortitis was the cause of the aortic regurgitation and diastolic murmur.
[2] Percentages for tachycardia are obviously low. Being common, the physicians did not deem it important to record in many instances.

This study does not provide conclusive evidence as to the reason that none of the 46 men had pain, but 20 of 28 men had congestive failure without recent myocardial infarcts or recent coronary thrombi, which may have accounted for the absence of pain in these men. Also, the percentage of men with "simple narrowing" of the coronary arteries (28 per cent) was significantly higher than among men with pain (11 per cent) Ten of the 13 men with "simple narrowing" had no gross myocardial infarcts.

Cardiac Signs. The number and percentage of patients with definite cardiac signs noted at the time of physical examination for 244 men who were hospitalized are presented in table 17. The percentages in this table

add to more than 100, since many patients had more than one sign of cardiac disease. Abnormal heart sounds were the most frequently noted. Gallop rhythm alone showed consistent decrease as age increased. Systolic heart murmurs also decreased slightly in the older age groups. Pericardial friction rub increased with advancing age, but the numbers involved were so small that no tests of significance were made. Cardiac enlargement increased significantly at age 40 and above, from 21 per cent in the youngest age group to 27 per cent in the age group 40 through 49, and 44 per cent in men aged 50 and over.

Electrocardiograms

Electrocardiograms were made for 49 of the 450 patients under 40 years of age, 81 of 250 in the 40 through 49 year group, and 125 of the 250 who were 50 years of age or over.

Many of the men died too suddenly for electrocardiograms to be made, or in places where they could not be obtained. The number made for each of these patients varied according to the length of survival, ranging from one to 11 per patient. In many cases only one or a few precordial leads

Table XVIII

Electrocardiographic Findings: Rhythm and Conduction Disturbances in Men with Coronary Artery Disease

Findings	Number in Age Group		
	18–39	40–49	50 and Over
Heart block			
First degree	—	1	5
Partial	1	1	3
Complete	—	5	4
Left bundle branch	—	4	8
Right bundle branch	2	7	8
Bundle branch (location unknown)	—	3	3
Intraventricular	1	3	3
Tachycardia			
Ventricular (paroxysmal)	—	3	5
Nodal	—	—	1
Ectopic beat			
Location not specified	—	1	5
Ventricular	—	6	10
Auricular	—	1	1
Nodal	—	1	1
Bigeminal and trigeminal rhythm	—	1	2
Auricular flutter	1	—	2
Auricular fibrillation	—	1	10
Bradycardia			
Sinus	—	1	2
Nodal	—	—	1
Total men with rhythm and conduction disturbances	4	28	53
Total men for whom electrocardiograms were made	49	81	125

TABLE XIX

Electrocardiographic Findings: Myocardial Lesions in Men with Coronary Artery Disease

Lesions	Number		
	18–39	40–49	50 and Over
Infarcts			
Location not stated	3	5	6
Anterior	15	21	32
Posterior	4	4	13
Anterolateral	—	—	1
Posterolateral	—	—	1
Anterior and posterior	3	6	5
Myocardial damage	18	15	30
Other abnormalities	1	8	25
Total men with myocardial lesions	44	57	106
Total men for whom electrocardiograms were made	49	81	125

were used, and in others the electrocardiograms were not made during the acute attack. These facts account for a diagnostic accuracy of only 44 per cent. The electrocardiographic findings are summarized in two tables showing separately the rhythm and conduction disturbances found (table 18) and the myocardial lesions diagnosed (table 19). Heart block was the most common major disturbance, its incidence increasing with age. Ectopic beats were noted much less frequently in the electrocardiograms than on physical examination (see table 17), no doubt because of their transient nature.

Infarcts, the most common myocardial lesion noted, occurred in 51 per cent of the patients 18 through 39 years of age who had electrocardiograms; in 44 per cent of those from 40 through 49 years, and in 46 per cent of those 50 years of age and over. The majority of infarcts in each group were situated anteriorly, and the percentages in this and other locations were not significantly different in the various age groups.

"Myocardial damage" was noted less frequently with increasing age, but the change was not significant. Indefinite statements that the electrocardiographic readings were indicative of myocardial abnormalities were recorded more often for the older than for the younger men.

Electrocardiographic and pathologic diagnoses did not always agree; however, the fact that in many cases not all the precordial leads were used probably accounts for the discrepancy. Accurate correlation was further hampered by the lack of data as to the times when the electrocardiograms were made in relation to the ages of the infarcts.

Course Subsequent to Onset of Terminal Illness

The course of 11 per cent of the 54 men under 40 years of age while in the hospital was described as asymptomatic, with death unexpected; whereas

in 26 per cent the course was "satisfactory," although symptoms were present and death was unexpected. Among 114 men from 40 through 49 years of age who were hospitalized, 16 per cent had an asymptomatic course and 20 per cent had a "satisfactory" course, with death unexpected. Among 137 men 50 years of age and over who were hospitalized, 7 per cent had an asymptomatic course and 14 per cent had a "satisfactory" course, with death unexpected. Thus, unexpected death with or without symptoms during the hospital course occurred less frequently with increasing age. In the other men, the course was progressively downward or "stormy," congestive failure increasing with age.

Pathologic Data

Descriptions of the gross pathologic changes in the 950 cases in this series lose some of their reliability for statistical purposes by reason of the fact that the findings at autopsy were recorded by many different individuals. However, since it seemed probable that errors in one direction might be partly or wholly counterbalanced by those in another, these descriptions were utilized in regard to cardiac hypertrophy, gross myocardial infarction and fibrosis, type of occlusion, involvement of arteries and other data. Blocks of tissue, paraffin blocks and slides were available for examination at the Armed Forces Institute of Pathology in 684 cases, as were tissues of the myocardium and one or more of the larger arteries. These were examined microscopically and the observations tabulated.

Size of Hearts. The weights of the hearts were noted in almost all cases and no statement was made of enlargement, and the assumption is made that weights not recorded might safely be regarded as normal. The degree of hypertrophy of the hearts was computed by reference to a table of normal heart weights in relation to body weights prepared by H. L. Smith [3]

Table XX

Grades of Hypertrophy in Men with Coronary Artery Disease

Grade of Hypertrophy	Per Cent in Age Group			
	18–29	30–39	40–49	50 and Over
No hypertrophy	68.	60.	50.	33.
Grade I	23.	27.	19.	19.
Grade II	7.	8.	11.	17.
Grade III	2.	3.	5.	14.
Grade IV	—	2.	5.	9.
Probable hypertrophy[1]	—	—	10.	8.
Total	100.	100.	100.	100.
Total patients with data	120	330	250	250

[1] Heart weight 400 gm. or over, body weight not given.

in 1928. The criteria used in computing the arbitrary degrees of hypertrophy were as follows:

Grade of Hypertrophy	Grams in Excess of Average
No hypertrophy	Below normal to 75 grams
Grade I	75–149 grams
Grade II	150–224 grams
Grade III	225–299 grams
Grade IV	300 grams and over
Probable hypertrophy	Heart weight 400 grams and over, body weight not recorded

As table 20 shows, the percentages for hypertrophy increased with age, the percentages of hearts hypertrophied grades 2 to 4, inclusive, being 9, 13, 21 and 40 for the four age groups. As observed in the article [1] concerning the men under 40 years of age, hypertrophy was not dependent upon the existence of hypertension in this group, but it may safely be concluded that some of the increase in the incidence of hypertrophy in the older groups was due to the additional factor of hypertension (see table 9).

TABLE XXI

Myocardial Infarcts in Relation to Size of Hearts in Men with Coronary Artery Disease

Myocardial Infarcts	Per Cent in Age Group							
	Normal or Hypertrophy under Grade II				Hypertrophy Grade II and Over			
	18–29	30–39	40–49	50 and Over	18–29	30–39	40–49	50 and Over
None	75.	70.	46.	39.	70.	51.	27.	24.
Gross	20.	25.	48.	39.	30.	42.	68.	54.
Microscopic[1]	5.	5.	6.	22.	—	7.	5.	22.
Total	100.	100.	100.	100.	100.	100.	100.	100.
Total men	110	287	182	129	10	43	68	121
Per cent of men in group	92.	87.	73.	52.	8.	13.	27.	48.

[1] Myocardial infarcts not described grossly, but noted on histologic examination.

Gross and microscopic myocardial infarcts occurred in higher percentages in all age groups for men with cardiac hypertrophy of grade 2 or more than for those with hearts of normal weight or hypertrophy of grade 1 (table 21). This increase in frequency of myocardial infarcts in conjunction with the higher percentages of older men with unmistakable hypertrophy indicated that infarcts were probably a factor in producing the hypertrophy in both the older and younger age groups; however, hypertension entered into the picture more prominently as age increased.

TABLE XXII

Ages of Gross Myocardial Infarcts in Men with Coronary Artery Disease

Ages of Infarcts	Per Cent in Age Group				Number in Age Group			
	18–29	30–39	40–49	50 and Over	18–29	30–39	40–49	50 and Over
Recent	57.	50.	45.	33.	15	42	58	33
Organizing	8.	12.	2.	7.	2	10	2	7
Recent and organizing	8.	7.	—	3.	2	6	—	3
Recent and old	8.	5.	23.	34.	2	4	30	34
Old	15.	24.	30.	19.	4	20	38	19
Organizing and old	4.	2.	—	4.	1	2	—	4
Unstated age					—	7	6	15
Total men with infarcts	100.	100.	100.	100.	26	91	134	115
Total infarcts					31	103	164	156

Gross Myocardial Infarcts. Table 22 shows the ages of myocardial infarcts described by the prosectors in the gross pathologic examination. Two observations of importance are revealed in these figures. First, multiple infarcts were found in relatively twice as many men aged 40 and over as in men under 40, although they did not appear significantly often except in the age group 50 and over. Second, the percentage of men with recent and/or organizing infarcts but no old infarcts decreased from 73 per cent in men under 30 years of age to 43 per cent in those aged 50 and over; thus, old infarcts alone, or in combination with recent and/or organizing infarcts, increased from 27 per cent in the youngest age group to 57 per cent in the oldest.

TABLE XXIII

Locations of Gross Myocardial Infarcts in Men with Coronary Artery Disease

Location of Infarct	Per Cent in Age Group				Number in Age Group			
	18–29	30–39	40–49	50 and Over	18–29	30–39	40–49	50 and Over
Left ventricle, without localization	19.	19.	22.	16.	5	17	30	18
Left ventricle, anterior wall	42.	30.	32.	35.	11	27	43	40
Left ventricle, apex and interventricular septum	19.	18.	7.	5.	5	16	9	6
Left ventricle, apex	8.	11.	23.	28.	2	10	31	32
Left ventricle, posterior wall	8.	11.	19.	19.	2	10	25	22
Left ventricle, lateral wall	—	5.	4.	2.	—	5	5	2
Interventricular septum, anterior third	4.	12.	23.	31.	1	11	31	36
Interventricular septum, posterior upper part	4.	4.	1.	1.	1	4	1	1
Right ventricle, posterior wall	12.	2.	10.	9.	3	2	13	10
Total men with infarction					26	91	134	115
Per cent of men in group	22.	28.	54.	46.				

The most common location of gross myocardial infarcts in all age groups was the anterior wall of the left ventricle (table 23). This location was noted more frequently in the 18 through 29 group than in the other age groups, as would be expected from the fact that the left anterior descending artery alone was occluded most often in that group. Infarcts located in the apex and interventricular septum combined were also more frequent in the youngest group. On the other hand, involvement of the anterior third of the interventricular septum alone and of the apex alone increased with age. Infarcts of the posterior wall of the left ventricle likewise increased with age, as did occlusion of the right coronary and left circumflex arteries. Other locations of infarcts were relatively uncommon.

Condition of the Coronary Arteries. Some inaccuracies in the description of the coronary arteries may have arisen from the fact that the various prosectors may not have examined all portions of the subepicardial coronary arteries. For example, 119, or 13 per cent, of the men in the series were reported as having neither sclerotic nor thrombotic occlusion of the coronary

TABLE XXIV

Comparison of Occlusion of Coronary Arteries in Men With Coronary Artery Disease

Occlusion	Per Cent in Age Group		Number in Age Group		
	18–39	40 and Over	18–39	40 and Over	Total
No occlusion	10.	14.	47	72	119
Thrombotic alone	37.	11.	167	54	221
Sclerotic and thrombotic	14.	36.	61	180	241
Sclerotic alone	39.	39.	175	194	369
Total	100.	100.	450	500	950

arteries, but only "simple" (moderate) narrowing of the lumens with thickening of the arterial walls. More extensive examination of the coronary arteries might have revealed either sclerotic or thrombotic occlusion, since 26 of these men had myocardial infarcts, and coronary artery disease was the only adequate cause of death in all of the 119 men.

Almost complete sclerotic occlusion alone of some parts of one or more coronary arteries was found in 369 (39 per cent) of the 950 men in the series; thrombotic occlusion alone in 221 (23 per cent), and both sclerotic and thrombotic occlusion in 241 (25 per cent) of the men. Table 24 is of particular interest, since it reveals that men under 40 years of age were much more apt to have thrombotic occlusion alone than those 40 years of age or over, and that the older men were more likely to have either "simple narrowing" of the coronary arteries without occlusion, or else both sclerotic and thrombotic occlusion. The percentages of men with sclerotic occlusion alone were approximately equal in men under 40 and those aged 40 years and over. The age group 50 years and over contributed the only significant number of deaths without occlusion.

TABLE XXV

Involvement of Coronary Arteries with Sclerotic or Thrombotic Occlusion in Men with Coronary Artery Disease[1]

Arteries Involved	Occlusion: Per Cent in Age Group							
	Sclerotic Alone				Thrombotic Alone			
	18–29	30–39	40–49	50 and Over	18–29	30–39	40–49	50 and Over
Left anterior descending	91.	81.	84.	79.	80.	78.	55.	59.
Right coronary	18.	26.	44.	41.	22.	20.	40.	35.
Left circumflex	20.	30.	36.	47.	17.	11.	20.	18.
Total men with occlusion	44	131	96	98	46	121	20	34
Per cent of men in group	37.	40.	39.	39.	38.	37.	8.	14.

[1] Percentages in this table add to more than 100, since sclerotic occlusion alone was present in more than one coronary artery in 136 men, and thrombotic occlusion alone in 23 men.

The left anterior descending artery was by far the most frequently affected by all types of occlusion (sclerotic, thrombotic, or both). However, involvement of this artery alone decreased with age, and there was a decided tendency toward involvement of this artery and either the right coronary or the left circumflex or both of these arteries also as age increased. The only exception was in involvement of the left circumflex artery in thrombotic occlusion alone. In this the incidence was almost equal for each age group.

Tables 25 and 26 illustrate this decrease in involvement of the left anterior descending artery alone, and the increasing involvement of the other two coronary arteries as age increased, regardless of whether only one or

TABLE XXVI

Involvement of Coronary Arteries with Both Sclerotic and Thrombotic Occlusion in Men with Coronary Artery Disease[1]

Arteries Involved	Occlusion: Per Cent in Age Group							
	Sclerotic				Thrombotic			
	18–29	30–39	40–49	50 and Over	18–29	30–39	40–49	50 and Over
Left anterior descending	79.	74.	87.	71.	86.	64.	69.	50.
Right coronary	21.	32.	51.	56.	14.	30.	36.	49.
Left circumflex	14.	32.	42.	40.	7.	11.	17.	21.
Total men with occlusion	14	47	108	72				
Per cent of men in group	12.	14.	43.	29.				

[1] Percentages in this table add to more than 100, since sclerotic occlusion was present in more than one coronary artery in 115 men and thrombotic occlusion in 39 men.

TABLE XXVII

Summary of Pathogenesis in Men with Coronary Artery Disease

Myocardial Infarction and Occlusion	Per Cent in Age Group				Number in Age Group			
	18–29	30–39	40–49	50 and Over	18–29	30–39	40–49	50 and Over
Without gross myocardial infarcts								
No occlusion, sclerotic or thrombotic	11.	8.	7.	15.	13	27	17	36
Sclerotic alone	34.	32.	21.	25.	41	107	53	63
Sclerotic and thrombotic	9.	8.	15.	11.	11	25	39	28
Thrombotic alone	24.	24.	3.	3.	29	80	7	8
With gross myocardial infarcts								
No occlusion, sclerotic or thrombotic	2.	1.	4.	4.	3	4	9	10
Sclerotic alone	3.	7.	17.	14.	3	24	43	35
Sclerotic and thrombotic	3.	7.	28.	18.	3	22	69	44
Thrombotic alone	14.	13.	5.	10.	17	41	13	26
Total	100.	100.	100.	100.	120	330	250	250
Total men with infarcts	22.	28.	54.	46.	26	91	134	115

both types of occlusion were found at autopsy. These tables present the grouped data showing the number of times each artery was involved.

Among men who had both types of occlusion, sclerosis of the right coronary artery alone occurred in 6 to 13 per cent, with no consistent age trend; and thrombotic occlusion of this artery, if associated involvement of the left circumflex artery be included, appeared with generally increasing frequency as age increased.

A summary of the pathogenesis of the coronary artery disease is presented in table 27. A majority of the men (584, or 61 per cent) had no gross myocardial infarcts.

Death without known occlusion of the coronary arteries occurred significantly more often in men who had no gross myocardial infarcts than in those with infarcts. Sclerotic occlusion alone also occurred more frequently

TABLE XXVIII

Ages of Coronary Thrombi in Men with Coronary Artery Disease[1]

Ages of Coronary Thrombi	Per Cent in Age Group			Number in Age Group		
	18–39	40–49	50 and Over	18–39	40–49	50 and Over
Recent[2]	88.	80.	69.	181	98	64
Recent[2] and old	2.	7.	9.	4	9	8
Old	10.	13.	22.	20	16	21
Total men with coronary thrombi	100.	100.	100.	205	123	93

[1] Includes 421 coronary thrombi of stated ages; an additional 41 were of unstated age.
[2] Includes both recent and/or organizing thrombi.

in those with no infarcts; but when sclerotic and thrombotic occlusion were found together, accompanying infarcts were noted more often than not.

Separate analysis of the age groups with respect to types of occlusion and absence or presence of gross myocardial infarcts indicated the following:

Thrombotic occlusion alone was a far more important factor in the death of men under 40 years of age than of men aged 40 and over, whether or not there were myocardial infarcts. Sclerotic and thrombotic occlusion occurring in the same patient were more important in the older than in the younger men, regardless of infarcts. "Simple narrowing" of the coronary arteries

TABLE XXIX

Ages of Coronary Thrombi in Relation to Thrombotic Occlusion with and without Infarction in Men with Coronary Artery Disease

Ages of Coronary Thrombi	Thrombotic Occlusion in Age Group[1]					
	Without Infarction			With Infarction		
	18–39	40–49	50 and Over	18–39	40–49	50 and Over
	Number					
Recent[2]	119	39	22	61	59	42
Recent[2] and old	—	—	3	4	9	5
Old	12	5	7	8	11	14
Total men with data	131	44	32	73	79	61
	Per Cent					
Recent[2]	91.	89.	69.	84.	75.	69.
Recent[2] and old	—	—	9.	5.	11.	8.
Old	9.	11.	22.	11.	14.	23.
Total men with data	100.	100.	100.	100.	100.	100.

[1] Includes thrombotic occlusion alone or with sclerotic occlusion.
[2] Includes recent or organizing thrombi, or both; 19 men who had multiple thrombi of these ages were each counted only once in this table.

occurred significantly often only in men 50 years of age and over who had no gross myocardial infarcts. There were no significant differences with respect to sclerotic occlusion alone among men in the older age group as compared to men under 40, whether or not infarcts were present.

It should be emphasized that thrombotic occlusion occurred in approximately one-half of the men in each age group, irrespective of the significance of the types of occlusion as factors contributing to death. It was found alone or in combination with sclerotic occlusion in 50 to 51 per cent of the men in each age group under 50, and in 42 per cent of the men aged 50 and over.

Ages of Coronary Thrombi. The ages of the coronary thrombi were

stated for 421 of the 462 men who had thrombotic occlusion alone or combined with sclerotic occlusion and are shown in table 28. The most important observation as to coronary thrombi was the decreasing percentage of recent thrombi alone as age increased. Sixty-nine per cent of the men who had old thrombi alone or combined with recent thrombi were 40 years of age and over. Also, when the ages of the coronary thrombi were considered in relation to thrombotic occlusion with or without infarcts (table 29), it was evident that recent or organizing thrombi or a combination of the two occurred in almost all the men who were under 40 years of age (91 per cent of those without myocardial infarcts, 84 per cent of those with infarcts), and that the percentages with thrombi of recent or comparatively recent origin (organizing) decreased with advancing age. Old thrombi alone or with recent thrombi were found in 9 per cent of the men under 40 years of age who had no myocardial infarcts, and in 16 per cent of those with infarcts. Corresponding percentages in the 40 through 49 year age group were 11 and 25, while 31 per cent of the men 50 and over, irrespective of the presence or absence of infarcts, had old coronary thrombi.

Grading of Atherosclerosis. Atherosclerosis was the important lesion of the coronary arteries of all age groups. However, there was a difference in the degree (age) of involvement among age groups as well as among individuals.

A somewhat arbitrary classification of the grades of atherosclerosis was made on the following basis:

Grade I: Early Atherosclerosis

1. Simple plaque formation, the plaque being composed of moderately loosely arranged connective tissue frequently containing young fibroblasts.
2. Absence of calcium.
3. Presence only occasionally of a small nidus of amorphous material in the plaque.
4. Slight, if any, vascularization of plaque or media.
5. Few, if any, cholesterol crystals in the plaque.
6. Slight to moderate damage to the internal elastic lamina, which usually may be identified.
7. Slight thinning with minimal interstitial fibrosis of the media below the plaque.

Grade II: Moderately Advanced Atherosclerosis

1. Hyalinized base of the plaque.
2. Presence of a large mass of amorphous cholesterol or lipid in the plaque.
3. Surface of plaque composed of compact fibrous tissue in which a few fibroblasts persist.

4. Minimal calcium deposition in center of plaque, usually in the form of fine calcium granules or calcified nuclei of fibroblasts.
5. Presence of a few cholesterol clefts.
6. Slight marginal vascularization.
7. Fragmentation or frequent absence of internal elastic lamina.
8. Moderately thin, occasionally vascularized media, with loss of muscle fibers and increased fibrosis below plaque.

Grade III: Advanced Atherosclerosis

1. Complete or almost complete hyalinization of the plaque, both base and surface zones, with fibroblasts remaining only at the margin.
2. Masses of calcium in plaques.
3. Frequent presence of cholesterol clefts.
4. Common presence of broad vascular channels at margin and base of plaque.
5. Absence of or severe damage to internal elastic lamina.
6. Hyalinization or atrophy of media, with loss of muscle and increase in fibrous tissue.

This tabulation of the features of the three grades of atherosclerosis reveals two general characteristics of the condition. First, the size of the plaque bears little relation to the age of the lesion. Second, cellular infiltration with lymphocytes and plasma cells either of the plaque or adventitia appears to be unrelated to age, although it is slightly more frequent in the recent lesions.

These criteria for the grading of atherosclerosis take into consideration the definite progression in degenerative changes of the media which accompany progressive severity of the atheromatosis. Thus, the relative age of the atheromatous plaque may be determined from the changes in the media.

On the basis of this grading of atherosclerosis, the distribution in the age groups under 40 years, 40 through 49, and 50 years and over is shown in table 30. The significant advance in the degree of atherosclerosis with increasing age of the patients is shown by the fact that advanced atherosclerosis (Grade III) occurred nearly twice as often in the age group 40 through 49 and more than twice as often among men 50 years of age and over as in the age group under 40 years. Although this method of grading differs somewhat from that of Leary,[4] it has the advantage of showing the progressive changes in degeneration of the media with the advancing degree of atherosclerosis, which permits determination of the relative age of the atheromatous plaque.

Unfortunately the data on the incidence of hemorrhage in atheromatous plaques are inadequate, since the correct incidence of this condition can be obtained only by the examination of multiple histologic sections of the coronary arteries, together with painstaking gross examinations of the opened

TABLE XXX

Distribution of Grades of Atherosclerosis in Men with Coronary Artery Disease

Grade of Atherosclerosis[1]	Per Cent in Age Group			Number in Age Group		
	18–19	40–49	50 and Over	18–39	40–49	50 and Over
Grade I	30.	1.	1.	91	1	2
Grade II	30.	24.	17.	93	36	27
Grade III	40.	75.	82.	124	114	135
Total men with data	100.	100.	100.	308	151	164

[1] Combinations of grades were as follows: Age group 18–39, Grade II includes 3 men with both Grades I and II; age group 40–49, Grade III includes 16 men with both Grades II and III, and 1 man with Grades I, II, and III; age group 50 and over, Grade III includes 1 man with both Grades II and III.

vessels. Our average of the percentages of incidence for the different age groups was about 15. Record was not kept as to whether all hemorrhages were in association with coronary thrombi. Had this situation existed (we are certain it did not), the percentage would be 30 for cases of coronary thrombi, since such thrombi occurred in approximately one-half of the cases of this series. This percentage is still much smaller than that given by Paterson [5] in his excellent research on this subject.

Histologic Study of Myocardial Infarcts. As table 31 shows, myocardial infarcts were observed in nearly one-half (331) of the 675 cases which were studied histologically. The percentages of men with these infarcts increased with advancing age, due largely to the higher percentage of recent infarcts in men 40 through 49 years of age and old infarcts in men 50 years of age and over.

TABLE XXXI

Myocardial Infarcts, Diffuse Fibrosis and Focal Scars Found on Histologic Examination of Men with Coronary Artery Disease

Lesion	Per Cent in Age Group			Number in Age Group		
	18–39	40–49	50 and Over	18–39	40–49	50 and Over
Infarcts[1]	29.	51.	79.	88	87	156
Recent	9.	31.	27.	27	52	53
Organizing	13.	12.	12.	40	21	23
Old	7.	8.	40.	21	14	80
Total men with data				308	170	197
Diffuse fibrosis	12.	33.	53.	38	56	104
Focal scars	22.	49.	76.	67	82	150
Total men with data				308	169	198

[1] Multiple infarcts were as follows: 18–39 age group, 3 recent and organizing; 1 recent and old; 4 organizing and old; 2 recent, organizing and old, 40–49 age group, 7 recent and organizing; 1 organizing and old; 2 recent, organizing and old. 50 and over age group, 7 recent and organizing; 4 recent and old; 13 recent, organizing and old.

*Histologic Study of Myocardial Fibrosis.** Both diffuse fibrosis and focal scars found microscopically increased greatly with increasing age, the former from 12 per cent in men under 40 to 53 per cent in men 50 years old or older, and the latter from 22 to 76 in these respective age groups.

Table 32 presents data on pericarditis and its association with both recent and/or organizing myocardial infarcts and with old infarcts, mural thrombi in men with myocardial infarcts, and rupture of the heart in men with recent and/or organizing infarcts, and ventricular aneurysms in men with old infarcts.

Pericarditis. The total number of men with pericarditis was 115; it was present in only 4 per cent of the men under 40 years of age, and in 19 per cent of those aged 40 and over. The incidence of recent myocardial

TABLE XXXII

Pericarditis, Mural Thrombi, Rupture and Ventricular Aneurysms in Men with Coronary Artery Disease

Conditions	Per Cent in Age Group			Number in Age Group		
	18–39	40–49	50 and Over	18–39	40–49	50 and Over
Pericarditis[1]	4.	18.	20.	20	44	51
Recent myocardial infarcts[2]	15.	24.	37.	13	22	30
Old myocardial infarcts[3]	24.	31.	28.	8	21	16
Mural thrombi[4]	37.	34.	56.	43	46	64
Rupture[2]	5.	3.	10.	4	3	8
Ventricular aneurysm[3]	12.	19.	21.	4	13	12

[1] Based on total men in series (18–39 years, 450; 40–49 years, 250; 50 and over, 250). In the 40–49 age group, 8 of the 44 men with pericarditis had no infarcts and 2 men had infarcts of undetermined age. Of the 51 men with pericarditis in the 50 and over age group, 13 had no infarcts and 3 had infarcts of undetermined age.

[2] Based on number of men with recent and organizing infarcts (18–39 years, 86; 40–49 years, 90; 50 and over, 81).

[3] Based on number of men with old infarcts (18–39 years, 33; 40–49 years, 68; 50 and over, 57).

[4] Based on total number of men with myocardial infarcts (18–39 years, 117; 40–49 years, 134; 50 and over, 115).

infarcts in association with pericarditis rose with increasing age. (Recent infarcts include recent and/or organizing infarcts; old include either old alone or in combination with recent or organizing infarcts.)

Mural Thrombi. Mural thrombi in men with myocardial infarcts tended to be more frequent at age 50 and over, the percentages being 37, 34 and 56, respectively, in the three age groups. The average figure as presented by Bean [6] is 45 per cent; only the men aged 50 and over exceeded this average, and both of the younger age groups in the table were well under average. Four additional patients in the 18 through 39 year age group had mural thrombi which were found on microscopic examination but were not de-

* This term applies to fibrosis or scars thought not to be scars of old infarcts but the result of transient myocardial ischemia.

scribed grossly. This was true of seven patients in each of the two older groups.

Rupture of the Heart. The hearts of four men in the 18 through 39 age group, three in the 40 through 49 age group, and eight in the age group 50 years and over were ruptured. In percentage form, these numbers represented more than twice as many ruptured hearts in the oldest age group (10 per cent) as in the younger groups (4 per cent).

Ventricular Aneurysm. The incidence of ventricular aneurysm increased with advancing age, from 12 per cent of the men 18 through 39 years old who had myocardial infarcts, to 19 per cent of those 40 through 49 years of age and 21 per cent of the men 50 years old and older.

Valvular Abnormalities. Valvular lesions were found in 11 men under 40 years of age, eight who were 40 through 49, and 11 men aged 50 and over. Mitral stenosis and/or aortic scars of rheumatic origin occurred in 10 men under 40 years of age, and in one man in the age group 40 and over. Rheumatic scars of the mitral and pulmonic valves were found in one man in the age group 40 through 49 years. Aortic stenosis not defined as rheumatic in origin occurred in three men who were age 50 and over.

Fifteen men had syphilitic aortitis, three with regurgitation. One of the men with regurgitation was under 40 years of age, the other two were 50 or more years old. The 12 men who had no regurgitation were divided evenly between those 40 through 49 and 50 years of age or over, although regurgitation may possibly have been present in one man in the former age group.

Atherosclerosis of the Aorta. Men 40 years and over differed significantly from those below 40 as to the presence of atherosclerosis of the aorta. The percentages in the older men were more than twice as high as in the youngest group, 97 and 98 per cent, respectively, among men aged 40 through 49 and 50 and over, as compared to 41 and 43 per cent, respectively, of men 18 through 29 and 30 through 39 years of age. Furthermore, not only the incidence but the extent and severity increased with age. However, on the whole the degree of atherosclerosis of the aorta was not nearly as great as the degree of atherosclerosis of the coronary arteries, although this discrepancy tended to decrease markedly after the age of 50.

Lesions in Other Arteries. Arteriosclerosis of the kidneys increased from 5 per cent in men under 40 years to 8 per cent among those 40 through 49 years, and 22 per cent of the men 50 years of age or over.

Cerebral arteriosclerosis was observed in about 4 per cent of the men under 40, 22 per cent of those 40 to 50 years of age, and 45 per cent of those 50 years old or older.

Despite the increasing importance of the arteriosclerosis in arteries other than those in the heart as age increased, the percentages of men with generalized arteriosclerosis do not seem sufficiently high to justify a conclusion that coronary artery sclerosis is part of a generalized arteriosclerotic process

in the majority. Although the arterial lesion is the same, there appears to be some unknown factor that makes the coronary arteries more susceptible than other arteries in many cases.

Renal Lesions. Nephrosclerosis occurred in 5 per cent of the men aged 18 through 39, 8 per cent of those 40 through 49, and 22 per cent of those 50 and over. Renal infarcts were found increasingly often with advancing age, but occurred in only 3 per cent of the men under 40, and 7 per cent of those 40 years of age and over.

Lesions in the Brain. The brains of 506 of the men were examined and 305, or 60 per cent, were found to be normal. However, the percentages with normal brain findings decreased from 76 in men under 40 years of age to 42 per cent in those 50 years old or older (table 33). Con-

TABLE XXXIII

Brain Findings in Men with Coronary Artery Disease[1]

Brain Findings	Occurrences							
	Per Cent in Age Group				Number in Age Group			
	18–29	30–39	40–49	50 and Over	18–29	30–39	40–49	50 and Over
Normal	76.	71.	55.	42.	50	131	71	53
Congestion, hyperemia, edema	21.	21.	19.	12.	14	38	25	15
Subarachnoid hemorrhage	—	2.	3.	1.	—	3	4	1
Arteriosclerosis	5.	4.	22.	45.	3	8	28	56
Infarcts	1.	2.	3.	4.	1	3	4	5
Cerebral hemorrhage	1.	1.	2.	2.	1	2	3	2
Total examined	55.	56.	52.	05.	66	185	130	125

[1] Percentages in this table add to more than 100, since a number of men had more than one brain finding.

gestion of the brain was the most frequent observation in the younger age groups, occurring in 21 per cent of the men under 40, in 19 per cent of those 40 through 49, and in 12 per cent of the men 50 years of age or over. In the two oldest groups, arteriosclerosis was by far the most frequent change in the brain, the percentages for the three groups being 4, 22 and 45. Cerebral hemorrhage occurred in a small percentage in each age group. The same was true of subarachnoid hemorrhage. Infarcts of the brain were found in 13 cases.

Congestion of Organs. Eighty-four per cent (751 men) of the 896 for whom data were available had some congestion of the viscera. There were no significant differences with respect to the presence of congestion in men under 40 as compared to those aged 40 and over (83 and 85 per cent, respectively).

Non-cardiac Infarcts. Ninety-four men had infarcts in sites other than the heart. Twenty of these men were in the age group under 40 years (4

per cent of the 450 men in the age group). Thirty-four men in the 40 through 49 year age group and 40 in the oldest group had non-cardiac infarcts, representing 14 and 16 per cent of the total in the respective age groups. They occurred in 1.4 organs per man in the age groups under 50 and 1.5 organs per man in the 50 and over age group. Table 34 presents pertinent information on non-cardiac infarcts.

There were no significant differences between age groups with respect to the ages of the non-cardiac infarcts. Multiple infarcts were found in approximately 70 per cent of the men in each age group.

TABLE XXXIV

Locations of Non-cardiac Infarcts in Men with Coronary Artery Disease

Locations of Infarcts[1]	Per Cent in Age Group			Number in Age Group		
	18–39	40–49	50 and Over	18–39	40–49	50 and Over
Lung	55.	56.	63.	11	19	25
Kidney	35.	44.	43.	7	15	17
Spleen	20.	21.	28.	4	7	11
Brain	20.	12.	13.	4	4	5
Extremity[2]	10.	9.	8.	2	3	3
Adrenal	5.	—	—	1	—	—
Total men with non-cardiac infarcts	4.	14.	1.6	20	34	40

[1] Non-cardiac infarcts found in more than one organ were in the following locations: 18–39 year age group: Pulmonary and renal in 2 patients; renal and spleen, 1; renal and adrenal in 1; spleen and brain in 1; and pulmonary, renal and brain in 1. 40–49 year age group: Pulmonary and renal in 3; pulmonary and spleen in 2; pulmonary and brain in 1; renal and spleen in 1; renal and extremity in 1; pulmonary, renal and spleen in 1; pulmonary, renal and brain in 1; and renal, spleen and extremity in 1. 50 years and over age group: Pulmonary and renal in 4; pulmonary and extremity in 1; renal and spleen in 2; pulmonary, renal and spleen in 3; pulmonary, brain and extremity in 1; renal, spleen and brain in 2; and renal, spleen, brain and extremity in 1. Multiple infarcts in one organ are counted only once in this table.

[2] Includes emboli.

Although pulmonary infarcts constituted 63 per cent of the infarcts in men 50 years and over, as compared to 55 and 56 per cent in men under 40 and those 40 through 49 years of age, the difference was not significant; nor did the occurrence of infarcts in any of the other organs appear to differ significantly in the various age groups, although cerebral infarcts constituted 20 per cent of the infarcts of the men 18 through 39 years of age and 12 and 13 per cent of those in the two older age groups.

Eighty per cent of the 94 men with non-cardiac infarcts also had infarction of the myocardium. These constituted approximately 22 per cent of the 366 men with gross myocardial infarcts, the percentages increasing from 14 in the age group under 40 years to 20 and 28 in the two older groups. In other words, these percentages, 14, 20 and 28, represented the incidence of non-cardiac infarcts in cases of myocardial infarction. The non-

cardiac infarcts were diagnosed clinically in only 26.5 to 35 per cent of men with such infarcts. Furthermore, only 35 to 40 per cent of the non-cardiac infarcts were regarded as having contributed to death.

Sixty-two to 70 per cent of the men with non-cardiac infarcts were found to have mural thrombi at autopsy (70 per cent in the age group 18 through 39, 61.8 per cent in the group 40 through 49 years, and 62.5 per cent of those 50 years old and older). The 60 men with both non-cardiac infarcts and mural thrombi represent 39 per cent of the 153 who had mural thrombi. Corresponding percentages in the three age groups were 33 in men under 40, 46 in men 40 through 49, and 39 in men 50 years old or older, but the differences did not prove to be significant. Non-cardiac infarcts not associated with mural thrombi were usually pulmonary infarcts, but in a few cases infarcts elsewhere occurred in the absence of mural thrombi and/or myocardial infarcts at autopsy.

TABLE XXXV

Associated Pathologic Conditions in Men with Coronary Artery Disease

Location	Number in Age Group		
	18–39	40–49	50 and Over
Respiratory system	186	144	240
Gastrointestinal tract	28	47	72
Liver and gall bladder	55	55	84
Genito-urinary system	68	90	251
Brain	14	17	23
Miscellaneous	48	49	84
Total men in series	450	250	250

Among the 55 men with pulmonary infarcts, 39, or 71 per cent, did not have mural thrombi in the right ventricle or the right auricle; the other 16 had mural thrombi in one or the other or both of these chambers. Ten of the 16 men were in the age group 50 and over.

Associated Pathologic Conditions. A tally was made of the majority of pathologic conditions other than those due to coronary artery disease in the men of different age groups (table 35). The number of lesions in all systems and/or organs increased with advancing age, particularly in men aged 50 and over. These lesions totaled 399, 402 and 754 for the three groups. Many men had multiple lesions. Most of these lesions did not contribute to the death of the men. For example, among the lesions of the respiratory system there were 187 instances of pleural adhesions and 79 of healed pulmonary tuberculosis. Table 36 lists the conditions that may have been contributory to death in addition to the coronary artery disease and the non-cardiac infarcts discussed above. The percentages of such conditions are 16, 32 and 72 for the three age groups. Only five of the 950 men were known to be diabetic.

TABLE XXXVI

Associated Pathologic Conditions Probably Contributory to Death in Men with Coronary Artery Disease

Location and Lesion	Number in Age Group		
	18–39	40–49	50 and Over
Respiratory System			
Pneumonitis	12	8	9
Active tuberculosis	7	5	5
Empyema	1	—	2
Lung abscess	—	1	1
Miliary tuberculosis	—	—	1
Organizing pneumonitis	—	—	2
Carcinoma, lung, primary	—	—	1
Carcinoma, lung, metastatic	—	—	1
Spontaneous pneumothorax	—	—	1
Gastrointestinal Tract			
Acute appendicitis	3	—	—
Peritonitis	1	1	—
Carcinoma, stomach	—	—	2
Pyloric stenosis	—	—	1
Incarcerated hernia	—	—	1
Acute pancreatitis	—	2	—
Adenoma, Islands of Langerhans	—	1	—
Liver and Gall bladder			
Portal cirrhosis	3	5	4
Choledocholithiasis	—	—	1
Jaundice	—	—	2
Genito-urinary System			
Nephrosclerosis	23	20	55
Prostatic hypertrophy	9	16	52
Pyelonephritis	1	—	2
Glomerulonephritis	1	—	2
Focal suppurative nephritis	—	—	1
Renal abscess	—	1	—
Carcinoma, renal	—	—	1
Carcinoma, bladder	—	—	1
Carcinoma, prostate	—	—	7
Malignant tumor, testis	1	—	—
Thrombosis, renal vein	—	—	1
Ureteral stricture	—	—	1
Brain			
Encephalomalacia	3	7	12
Glioma, ependymal	1	—	—
Subarachnoid hemorrhage	3	4	1
Cerebral hemorrhage	3	3	2
Miscellaneous			
Pheochromocytoma	1	—	1
Diabetes mellitus	—	3	2
Gangrene, foot and leg	—	1	—
Cellulitis, foot	—	1	—
Aortic abscess, miliary	—	1	—
Aortic thrombosis	—	1	1
"Diabetic" gangrene	—	—	1
Buerger's disease	—	—	1
Thrombosis, inferior vena cava, incomplete	—	—	1
Total conditions	73	81	179
Per cent	16.	32.	72.
Total men in series	450	250	250

Comparative Prognosis

We may now utilize the data we have collected for the purpose of comparing the prognoses of coronary artery disease for the several age groups. Such a comparison based on these data cannot be entirely satisfactory, for soldiers are discharged or retired from the Army because of cardiac disease, and these men are not included in this analysis. However, some differences among the age groups are sufficiently striking to warrant generalizations.

It was noted that the younger men were much more likely to die suddenly without previous indication of cardiac disease, whereas the older men more often survived episodes of myocardial infarction and other manifestations of heart disease. There was also a tendency toward longer survival following the terminal acute "attack" as age advanced. The incidence of cardiac hypertrophy increased progressively with age and was greater than would be accounted for by the progressive increase in the incidence of hypertension. As age advanced there were also greater incidences of old myocardial infarcts and of multiple myocardial infarcts, as well as of both diffuse and focal scars of the myocardium. There was a progressive trend toward more extensive and more severe involvement of the coronary arteries as age increased; this trend was striking in regard to the greater degree of atherosclerosis and the incidence of old thrombi in the coronary arteries. The frequency of associated pathologic conditions that might have contributed to death increased greatly with advancing age. This array of facts indicates that coronary artery disease is a more serious threat to life the younger the individual that acquires it. In other words, the later in life the disease develops, the greater the tolerance to it. Probably it is a more slowly progressive disease on the whole in older men, allowing more time for the development of the coronary collateral circulation.

Summary

A study has been made of 950 autopsied cases of coronary artery disease with the objective of comparing the clinical and pathologic aspects of the disease at different age periods. The patients were mainly male soldiers; a small number were civilians. There were 120 men aged 18 through 29 years, 330 aged 30 through 39 years, 250 aged 40 through 49 years, and 250 aged 50 and more years.

Negroes comprised only 4 per cent of the World War II soldiers in the series, although they constituted approximately 10 per cent of the Army during that period.

Among the men who entered the Army during World War II the men aged 30 and over tended to die earlier in their Army careers.

In the entire series there was an apparent tendency toward overweight with advancing age, but the etiologic importance of the factor could not be definitely established in any age group.

Hypertension was recognized in 4 per cent of the men under 40 years of age, 13 per cent of those 40 through 49, and 23 per cent of those 50 and over.

The onset of the "coronary attack" occurred in a higher percentage of the younger men while they were engaged in strenuous activity, and in a higher percentage of the older men while they were in bed.

The men aged 40 and over more often gave a history of "premonitory" symptoms or of manifestations of coronary artery disease three weeks or more before the onset of final illness. "Fatal attacks" were more likely to occur without warning in men under 40 years of age.

The majority of the men under 50 had no myocardial infarcts, even though there was a history of previous manifestations of cardiac disease. Myocardial scars, alone or in conjunction with myocardial infarcts, increased with age when there was a previous cardiac history.

Previous congestive failure, dyspnea, and attacks of clinically diagnosed myocardial infarction had occurred more often in men aged 40 and over than in those under 40. The duration from the onset of the attacks of coronary insufficiency was longer in the older than in the younger men.

More men for whom information was available had experienced angina of effort beginning six months or more before the onset of the fatal illness than within the six months immediately preceding this illness.

Myocardial infarcts increased in frequency with advancing age in those men who had a history of attacks of coronary insufficiency. In cases in which congestive failure had occurred the finding of myocardial infarcts decreased percentage-wise with age, contrary to expectation. Hypertension also appeared to be an unimportant factor among the men who had congestive failure.

There was a tendency toward longer survival following the acute "coronary attack" as age increased. Men aged 40 and over with a previous cardiac history appeared to survive 24 hours or longer more often than those under 40. Men under 40 with occlusion and no myocardial infarcts were more likely than the older men to die within 24 hours; men aged 40 and over who had occlusion with infarcts tended to survive for one day or longer.

Pain was the most frequently noted symptom of the terminal illness, but its incidence decreased from 98 per cent to 84 per cent with age. Manifestations of shock were second in order of frequency. "Collapse" occurred significantly more often in the men under 40 than in those aged 40 and over. The reverse was true of cyanosis. Respiratory symptoms, congestive failure and embolization increased with age, whereas gastrointestinal symptoms and those referable to the central nervous system were more common in the younger men.

As to cardiac signs, the incidence of gallop rhythm and systolic murmurs decreased with age, whereas the incidence of pericardial friction rub and cardiac enlargement increased with age, the latter greatly.

A study was made of the 46 men who did not have pain. These men

were older and tended to live longer than those with pain. Congestive failure was more common among men without pain than among those with pain, and its incidence increased with age.

Disturbances of rhythm and conduction as noted on electrocardiographic examination increased with age. Electrocardiographic diagnoses of the site of infarction showed a great preponderance of anterior location.

Unexpected death with or without symptoms in those men in the entire series who were hospitalized occurred less frequently with advancing age.

In regard to pathologic data, cardiac hypertrophy increased with age far more than could be accounted for by the increasing incidence of hypertension. Myocardial infarcts increased with age among those men with cardiac hypertrophy. Thus it appeared that the more damaged the myocardium, the more often cardiac hypertrophy occurred, and this trend increased definitely with age.

The incidence of myocardial infarcts increased greatly with the advance in age up to the age of 50 years and then decreased moderately.

Recent and/or organizing myocardial infarcts decreased with age, whereas old infarcts with or without recent or organizing infarcts increased with age. The older men were more inclined to have two or more infarcts. The infarcts in men under 30 were located more commonly in the anterior wall of the left ventricle; posterior infarcts increased with age.

Men under 40 years of age were much more apt to have thrombotic occlusion alone in the coronary arteries than were older men; the older men were more likely to have either "simple narrowing" of the arteries or sclerotic and thrombotic occlusion together. Sclerotic occlusion alone occurred with about equal frequency in all age groups.

Although the left anterior descending artery was by far the most frequently affected by occlusion (sclerotic, thrombotic, or both), there was a decided tendency toward involvement also of the right coronary or the left circumflex artery or both as age increased.

Recent and/or organizing thrombi alone decreased with age, whereas old thrombi with or without recent and/or organizing thrombi increased with age.

When atherosclerosis of the coronary arteries was graded as to degree (age) of involvement, it was found that there was a great advance in the degree of the atherosclerosis with increasing age of the men.

Mural thrombi, fibrosis of the myocardium, rupture of the heart, ventricular aneurysm, and pericarditis in association with recent myocardial infarcts, all showed greatly increased incidence with age.

Atherosclerotic lesions of arteries other than those of the heart increased with age, notably in the aorta, kidneys and brain.

Non-cardiac infarcts found at autopsy, mainly of embolic origin, increased from 4 to 16 per cent with age whether there were myocardial infarcts or not. Considering only those men with myocardial infarcts who

had non-cardiac infarcts, the percentages increased from 14 to 28. When men with mural thrombi were considered, it was seen that non-cardiac infarcts occurred in percentages ranging from 33 to 46. Among the men with pulmonary infarcts, 71 per cent did not have mural thrombi in the right side of the heart. In only about a third of the men with non-cardiac infarcts were such infarcts diagnosed during life, and only about two-fifths of the non-cardiac infarcts were thought to have contributed to death.

Lesions other than infarcts outside of the heart increased greatly with age. Many of these were of no particular significance, but the number of lesions which may have contributed to the deaths of the men increased greatly with age.

The accumulated data indicate that coronary artery disease carries a more serious prognosis for men under 40 than for men aged 40 and over.

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TREATMENT OF CHRONIC BLOOD DONOR ANEMIA *

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THE composition of a molecule of hemoglobin is 96 per cent protein in the form of globin. According to Schmidt,[1] globin contains 15 amino acids, with lysine and histidine comprising 45 per cent of the amino acid total. In studies on anemic dogs, however, Whipple [2] demonstrated that feedings of specific amino acids did not result in hemoglobin regeneration in proportion to the component of the particular acid in globin. This fact emphasizes the complex process of globin synthesis in the body.

It is understandable that limitation of available dietary protein might not only result in anemia but might also slow the regeneration of hemoglobin following bleeding. Hahn and Whipple [3] showed that protein intake, when limited, can restrict the production of hemoglobin in anemic animals. The fact that in human beings anemia due primarily to dietary protein deficiency is not more common may be related to the favored position held by globin in the protein pool. Robscheit-Robbins, Miller and Whipple found that doubly depleted dogs (hypoproteinemic and anemic) invariably produce more hemoglobin than plasma protein on all types of diets. Acceleration of blood regeneration by adequate intake of protein in rats and dogs made anemic by repeated hemorrhage has been demonstrated.[4, 5, 6]

An unusual opportunity for the study of this problem in man presented itself when a group of patients suffering from severe anemia caused by multiple blood donations were admitted to the Third Medical Division of Bellevue Hospital. The severity and the etiology of the anemia observed were puzzling features until one patient boasted of having sold his blood approximately 24 times in one year. Similar histories were subsequently elicited from all of the other patients except one (E. S.). Since no evidence of acute or chronic bleeding could be found, and his response to treatment was characteristically dramatic, it was assumed that this man was also a chronic blood donor. All of the patients studied had histories of chronic alcoholism and, although none appeared malnourished, their diets were probably inadequate.

METHODS

The following procedures were employed:

1. Hemoglobin determination by the acid hematin method, using a Klett Newcomer colorimeter.

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2. Red and white blood cell counts done in the usual way.

3. Reticulocyte counts made on dried stained smears prepared by mixing equal quantities of capillary blood and a saline solution of cresyl blue.

4. Plasma protein determination by the micro-Kjeldahl standard Howe method.

5. Plasma iron determination by the method of Kitzes, Elvehjem and Schuette.[7]

Material

Eleven patients were studied. They were all white males, with ages ranging from 34 to 57 years. Their symptoms, listed in table 1, fall into two groups. Four patients (E. R., W. B., J. R., and B. C.) had respiratory complaints. In one of them (B. C.) cough had been present for over a year and was apparently due to chronic pulmonary damage. His symptoms of weakness and dyspnea were of recent origin and cleared up with disappearance of anemia. Of the other patients with cough, two (E. R. and W. B.) had roentgen-ray evidence of bronchopneumonia, and one (J. R.) had an upper respiratory infection. One patient (C. F.), who was admitted with the complaint of repeated syncope, had roentgen-ray findings of right middle lobe pneumonia and a high white blood count. The anemia associated with respiratory disease was not treated until the patients had recovered from their acute infection.

Table I

Admission Symptoms of 11 Patients with Severe Anemia.

Patient	E. R.	C. F.	W. B.	W. M.	J. E.	D. B.	A. N.	M. G.	B. C.	E. S.	J. R.
Weakness			X	X	X	X		X	X	X	
Dyspnea					X		X		X	X	
Dizziness				X	X			X			
Fainting spells		X		X	X						
Cold sweats				X							
Anorexia					X						
Diarrhea											X
Vomiting											X
Cough	X								X		X
Chest pain	X		X								
Chills and fever	X		X								

In the second group, severe weakness was the chief complaint of all seven patients. It was accompanied by dizziness in three. Dyspnea was present in four cases, fainting spells in three. These symptoms were, in retrospect, considered to be the result of severe anemia, since all disappeared with improvement of the hematologic state. One patient (E. S) had been treated for congestive failure by his private physician, but his weakness and dyspnea had not responded to the digitalis, barbiturates or vitamins which he had received prior to hospital admission. In one month his hemoglobin rose from 4.7 to 10.3 gm. per cent on a regimen of ferrous sulfate, vitamins, a

high calorie diet and one transfusion. His symptoms subsided completely and, when seen in the clinic one month later, he was essentially a well man. One patient had symptoms referable to the gastrointestinal tract. These were associated with an upper respiratory infection and a cough. They subsided in a couple of days without specific therapy.

Discussion

The blood counts taken at the beginning of this study are listed in table 2. The hemoglobin determinations ranged from 3.4 to 7.5 gm. per cent, all less than half of the normal average figure for adult males (i.e., 16 gm. per cent). Hypochromia was marked in all cases, microcytosis present nine times. One patient only (E. R.) had macrocytosis. This patient had reversal of his A/G ratio and, like the entire group, a history of steady heavy drinking. The macrocytic character of his red blood cells is characteristic of that associated with cirrhosis.[9, 10]

Table II

Character of Blood Picture Prior to Institution of Therapy for Anemia.

	Blood Counts Before Beginning Therapy											
Patient	E. R.	C. F.	W. B.	W. M.	J. E.	D. B.	H. N.	M. G.	B. C.	E. S.	J. R.	Normal Figures (8)
Hb in gm.%	7.5	6.3	4.2	6.4	6.0	3.4	5.8	4.9	6.0	4.7	6.0	16.0 ± 2.0
RBC in millions	3.39	3.76	2.28	3.23	3.00	2.21	3.43	3.21	3.39	3.06	2.83	5.4 ± 0.8
WBC in thousands	9.7	6.1	9.4	10.1	—	9.7	8.3	8.7	7.1	6.0	7.3	5.0 — 10.0
Hematocrit	36	23	18	26	—	16	27	24	26	22	26	47 ± 7.0
Reticulocytes %	1.6	3.0	3.5*	1.2	—	1.4	0.6	0.6	1.4	2.4	1.0	0.5 — 1.5
MCV cu	107	61.1	78.9	80.5	—	72.3	78.7	74.7	76.6	71.8	91.8	87 ± 5
MCHb γ	22.0	16.7	18.2	19.8	20.0	15.5	16.9	15.2	17.7	15.3	21.2	29 ± 2
MCHbC %	20.8	27.3	23.1	24.6	—	21.0	21.4	20.4	23.0	21.3	23.0	34 ± 2
Plasma iron μ gm.%	56	55	165*	55	—	29	37	31	35	26	12	80 —150

* Patient had been on ferrous sulfate for two days.

Only three patients had a slight elevation of reticulocytes. This fact suggests that, even in the face of the stimulation from recent blood loss, hematopoiesis was depressed. In the light of subsequent response to therapy it became apparent that this depression resulted from inadequate material for blood regeneration.

The plasma iron determinations were well below the normal range of 80 to 150 micrograms per cent, except in the case of one patient (W. B.), who had received ferrous sulfate for two days before he came to our attention. Low plasma iron levels are characteristic of iron deficiency anemia, whether the latter is due to chronic hemorrhage or some other cause.[11, 12]

The response to therapy is summarized in table 3, in which are also listed the admitted blood "donations." The latter range from occasional to 29 times in two years. The practice of selling blood for a small fee was dis-

TABLE III

Response to Treatment in Hemoglobin, Red Blood Count, Plasma Proteins and Weight.

Pt.	Age	Blood Donations Admitted	Date	Hb. gm.%	R.B.C. in Millions	Hematocrit	Reticulocytes %	Plasma Fe μ gm.%	Plasma Proteins			Wt.	Therapy
									Total gm.%	Glob. gm.%	Alb. gm.%		
E. R.	40	25× in 2 years	12/17/45	7.5	3.39	36	1.6	56	6.67	3.84	2.83	144	—
		Weekly ×3	12/19/45	—	—	—	—	—	—	—	—	—	$FeSO_4$ 1 gm. t.i.d.
		Before admission	12/26/45	8.7	4.11	37	7.0	365	7.40	4.01	3.39	—	Amigen 100 gm. Nutramigen 100 gm.
			1/17/46	14.2	4.82	48	—	105	7.40	3.45	3.95	154	Discharged
C. F.	41	6× during past year	12/20/45	6.3	3.76	23	3.0	55	5.46	2.49	2.97	153	$FeSO_4$ 0.2 gm. t.i.d.
			12/27/45	8.4	3.80	32	7.0	247	7.18	3.96	3.22	—	Amigen 100 gm. Nutramigen 100 gm.
			1/25/46	12.0	4.99	42	1.7	112	7.09	2.89	4.10	157	Discharged
W. B.	34	2× in 6 months	1/6/46	—	—	—	—	—	—	—	—	—	$FeSO_4$ 0.2 gm. b.i.d.
			1/8/46	4.2	2.28	18	3.5	165	7.09	3.59	3.50	—	—
			1/16/46	5.8	2.97	26	—	50	6.80	2.86	3.94	—	Amigen 100 gm. Nutramigen 100 gm.
			1/31/46	9.9	3.90	40	3.0	62	7.27	2.92	4.35	—	Discharged
W. M.	41	5× during past year	12/7/45	6.4	3.23	26	1.2	55	7.10	3.81	3.29	—	$FeSO_4$ 0.2 gm. t.i.d.
			12/14/45	6.8	4.06	32	6.2	181	7.41	3.43	3.98	—	Nutramigen 200 gm.
			12/17/45	—	—	—	—	—	—	—	—	—	Nutramigen 400 gm.
			12/26/45	10.2	—	39	1.0	255	7.46	3.21	4.25	—	Discharged

TABLE III—*Continued*

TABLE III—*Continued*

Pt.	Age	Blood Donations Admitted	Date	Hb. gm.%	R.B.C. in Millions	Hematocrit	Reticulocytes %	Plasma Fe μ gm.%	Plasma Proteins			Wt.	Therapy
									Total gm.%	Glob. gm.%	Alb. gm.%		
J. E.	43	5× in 1944 24× in 1945	11/10/45	6.0	3.00	—	—	—	—	—	—	—	$FeSO_4$ 0.2 gm. t.i.d.
			11/20/45	8.3	3.22	34	—	332	6.70	2.75	3.95	—	—
			11/30/45	9.7	4.34	40	—	361	6.24	2.25	3.99	121	High protein diet
			12/10/45	—	—	—	—	—	—	—	—	—	Nutramigen 200 gm.
			12/29/45	12.8	4.34	44	—	180	6.52	2.78	3.74	121.5	Discharged
D. B.	37	Occasional (also history bleeding hemorrhoids)	4/17/46	3.4	2.21	16	1.4	29	6.42	3.67	2.75	—	$FeSO_4$ 0.6 gm. t.i.d.
			5/23/46	8.2	3.93	34	—	88	7.90	4.80	3.10	—	Discharged
H. N.	44	1× in 1946 10× in 1945 1-2× in 1944	2/12/46	5.8	3.43	27	0.6	37	7.41	3.34	4.07	170	$FeSO_4$ 0.2 gm. t.i.d.
			2/26/46	8.6	4.59	38	6.5	67	7.25	3.03	4.22	171	Discharged
M. G.	57	2× in April, 1945	1/23/46	4.9	3.21	24	0.5	31	6.91	3.54	3.37	162	Ward diet
			2/7/46	4.8	3.50	25	2.8	37	7.57	3.40	4.17	—	$FeSO_4$ 0.4 gm. t.i.d.
			2/25/46	8.4	4.08	35	2.4	67	7.64	2.89	4.75	176	Discharged
B. C.	48	22× in 3 years	2/12/46	6.0	3.39	26	1.4	35	6.41	3.35	3.06	—	$FeSO_4$ 0.2 gm. t.i.d.
			2/26/46	10.2	4.62	39	4.7	130	6.74	3.51	3.23	—	Discharged
E. S.	39	Denied	2/5/46	4.7	3.06	22	2.4	26	6.17	3.24	2.93	—	$FeSO_4$ 0.2 gm. t.i.d.
			2/14/46	—	—	—	—	—	—	—	—	—	500 c.c. blood IV.
			3/4/46	10.3	4.67	41	1.2	70	7.27	3.36	3.91	—	Discharged
J. R.	48	3× past 6 mos. Up to 2× week in year prior	2/1/46	6.0	2.83	26	1.0	12	6.24	2.44	3.80	142	Amigen 100 gm. Nutramigen 100 gm.
			2/25/46	6.0	3.40	26	1.5	67	6.82	2.62	4.20	150	Discharged on iron

covered, as previously stated, when one patient boasted of his many donations. The other patients were all reluctant and rather ashamed to admit such practice and did so only when confronted with a direct question. One (B. C.), for example, earned a good salary but didn't want his wife to know how much money he was spending for liquor, so he sold his blood to obtain extra funds for this purpose. It was our impression that, on the whole, the number of donations were more than stated in most cases.

Ten patients received ferrous sulfate therapy (0.6 to 3.0 gm. daily), with a prompt reticulocyte response in all patients. There was an early, rather marked elevation of plasma iron in most cases; this subsequently fell to lower levels. Five patients had plasma iron levels below normal on discharge, indicating a need for further therapy. This does not include one (J. R.) who received no iron while in the hospital. Like another patient (M. G.) who received no iron therapy for two weeks, his hemoglobin and hematocrit remained stationary.

There was prompt response in hemoglobin after the administration of iron. Hahn et al.[18] report that formation of hemoglobin in dogs made anemic by repeated bleeding takes place at a rapid rate. Radioactive iron is detectable in the circulating red blood cells four hours after feeding, and absorbed iron is entirely converted into hemoglobin within four to seven days under standard anemic conditions.

Six patients received protein supplement to a basic ward diet which contained approximately 90 gm. of protein and 2,500 calories. The patient (J. E.) who received the lowest protein supplement was on a high protein diet calculated as offering 130 gm. of protein daily. The protein supplement was given in the form of amigen or nutramigen, in amounts equivalent to 100 gm. of protein in four cases, 58 in one, and 29 in one. Five patients had a preliminary period of iron therapy alone. One (J. R.) who was given protein supplement but no iron gained eight pounds and showed an improvement in his plasma proteins (albumin from 3.80 to 4.20 gm. per cent) in 24 days. The fact that his hemoglobin remained unchanged illustrates the limiting rôle played by iron in hematopoiesis.

Elevated plasma globulin was present in all of these patients; in seven there was a reversal of the A/G ratio. This finding, plus the presence of a positive cephalin flocculation test in three men (D. B., H. N. and B. C.), suggested a diagnosis of cirrhosis.[10] Ten of the patients showed an increase in plasma albumin levels of a magnitude ranging from 0.15 to 1.38 gm. per cent. This improvement occurred regardless of the presence or absence of protein supplement in the diet.

The total and daily increase in hemoglobin levels during iron therapy alone and during iron and supplemental therapy is given in table 4. There was no hemoglobin formation in one patient (J. R.), who received protein without iron. This man had an extremely low plasma iron content, suggesting complete depletion of reserve iron with resultant inability to form new hemoglobin even in the presence of all other essential factors.

The dose of iron in the other patients (from 0.4 to 3.0 gm. daily) seemed unrelated to the amount of hemoglobin formation. Hahn [18] found better utilization in general of small doses of iron in anemic dogs. In our series of cases, the patient who received the smallest daily dose (0.4 gm.) had an average daily increase of hemoglobin of 0.20 gm. per cent, while the man who received the largest daily dose (3.0 gm.) produced only 0.133 gm. per cent of hemoglobin daily. We could not correlate the rapidity of response to therapy and the degree of anemia originally present. However, we are cognizant of the possible multiple factors present in these patients (i.e., presence and extent of liver disease, recent infection, general health and nutritional background, etc.), and feel this point cannot therefore be properly evaluated.

TABLE IV

Total and Average Daily Hemoglobin Production in 10 Patients Receiving Ferrous Sulfate Alone and in Five Patients Who Later Were Given Ferrous Sulfate and Protein Supplement in Their Diets. (J. B., who was given only protein supplement, manufactured no hemoglobin.)

Patient	$FeSO_4$ Therapy		Increase Gm. Hb.		Protein Supplement		Increase Gm. Hb.	
	Daily Dose in gm.	No. Days	Total	Daily	Gm.*	No. Days	Total	Daily
E. R.	3.0	9	1.2	0.133	100	22	5.5	0.250
C. F.	0.6	7	2.1	0.300	100	29	3.6	0.124
W. B.	0.4	8	1.6	0.200	100	15	4.1	0.273
W. M.	0.6	7	0.4	0.056	58	12	3.4	0.283
J. E.	0.6	20	3.7	0.185	28	29	3.1	0.106
D. B.	1.8	36	4.8	0.133	—	—	—	—
H. N.	0.6	14	2.8	0.200	—	—	—	—
M. G.	1.2	18	3.6	0.200	—	—	—	—
B. C.	0.6	14	4.2	0.300	—	—	—	—
E. S.	0.6	27	5.6	0.203	—	—	—	—
J. R.	—	—	—	—	100	24	—	—
Average	1.0	16	3.0	0.188	77.2*†	21.4*†	3.9	0.184

* Average daily intake as amigen and/or nutramigen supplement to $FeSO_4$ therapy.
† Excluding J. R., who received no $FeSO_4$.

There was a daily average increase of 0.188 gm. per cent of hemoglobin, with a range of 0.056 to 0.300 in all patients receiving ferrous sulfate. The latter figure, which we found in two cases (C. F. and B. C.), is equivalent to approximately 2 per cent hemoglobin (14.5 gm. per cent equals 100 per cent). Addition of 28 to 100 gm. daily of protein in an easily assimilable form resulted in an average daily output of 0.184 gm. per cent hemoglobin, with a range of 0.106 to 0.283. These figures are lower than those obtained on ferrous sulfate therapy alone. However, it will be noted that three patients (E. R., W. B. and W. M.) actually produced more hemoglobin daily when on a combined iron and protein regimen than when given iron only. One (W. M.) raised his daily increment from 0.056 gm. per cent to 0.283 gm. per cent hemoglobin when 58 gm. of protein were added to his daily diet and iron therapy. This fact is the more interesting in the light of

the finding by Robscheit-Robbins and Whipple [14] that hemoglobin production in dogs runs parallel to the degree of anemia. Additional protein in the diets of some of these patients apparently accelerated hemoglobin formation, even though their anemia was somewhat less severe at the time when protein was given in conjunction with iron than when iron alone was administered. We recognize, however, the fallacy of drawing conclusions from such a small series of cases and the possible presence of other factors.

Summary and Conclusions

1. Eleven patients with severe anemia resulting from frequent blood donations were studied.

2. This anemia was characterized by hypochromia, low plasma iron levels, absence of appreciable reticulocytosis and, in most cases, by microcytosis. These findings suggest exhaustion of body iron stores.

3. Iron therapy by mouth, even in small doses, produced dramatic responses.

4. High protein alimentation alone was ineffective, but when given in conjunction with iron accelerated hemoglobin regeneration in some cases.

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VOLUNTARY "UNILATERAL BREATHING"*

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Introduction

It is possible for an individual to control the respiratory movements of the chest wall to a marked degree. With a moderate amount of training one can learn to hold one side of the chest relatively motionless while making quite marked respiratory movements with the other side.

This fact has been utilized by physical therapists for some years in an effort to secure differential mobility of portions of the chest wall. Various unilateral and segmental breathing exercises have been devised to overcome residual immobility and deformity after injuries or operations affecting the chest wall. These exercises have also been recommended after empyema, lobectomy, etc., in an effort to reëxpand the involved lung or the remaining lobe or lobes. In addition, this type of exercise has been recommended to aid in the reëxpansion of spontaneous pneumothorax.

The present study has been made in an effort to learn to what degree the unilateral chest wall movements are translated to the underlying lung. Eight patients have been trained to breathe with one side of the chest and have had bronchospirometric studies made while breathing normally and then differentially. Three patients who were receiving artificial pneumothorax were trained in unilateral breathing and were then studied fluoroscopically and by means of intrapleural manometric readings.

Method of Training

The patient is told that, while respiration occurs automatically, the muscles of the chest wall are under his voluntary control. He places his hands upon the ribs and notices their movements with respiration. He is then urged to attempt to move one side only. At first he is allowed to make considerable pressure upon the side to be immobilized, using his hand for this purpose, but as the skill in control of his chest wall increases this aid is no longer necessary. Even with normal lungs not every person can learn this control, as may be the case with other muscular feats, inasmuch as a certain aptitude is required. Another obstacle to developing this skill is extensive unilateral pleural or pulmonary disease. In such a case the involved

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side may become largely immobilized by itself, and differential breathing is then impossible.

The 11 patients included in this study were all young males. Each one was trained for a period of one to three weeks. Three other patients who were to be included in the investigation were unable to develop sufficient control of the chest wall to perform the various tests satisfactorily.

Inspection and Mensuration

Five of the 11 men had excellent chest wall control. This was unilateral in some and bilateral in others. When requested to do so, these patients could make vigorous respiratory movements with one side of the chest, holding the other completely stationary by direct control (that is, without using the arm or hand to aid in the immobilization).

Table I

(Sample measurements* are given)

Case 1	At rest	Right 19″	Left 18½″
	Deep "bilateral" breathing	Right 19½″	Left 19″
	Voluntary "unilateral" breathing:		
	With right chest	Right 19½″	Left 18½″
	With left chest	Right 19″	Left 19″

* Made from the spine to the midline anteriorly just below the nipple.

In the above figures we see an arithmetical expression of the fact that the patient can at will expand either side of the chest while holding the other side immobile.

It must be stated that less control is shown over the upper portion of the chest. While the upper chest in any case expands less than the lower, none of the men studied could completely immobilize the upper portion of the chest. However, a definite decrease in the mobility was visible here when "unilateral breathing" was attempted.

Only about one-half of the patients could achieve complete immobility of one hemithorax. The remainder could secure marked but not complete immobility. An observer who did not know in advance which side was to be immobilized could detect in each case a well marked difference between the respirations of the hemithoraces during the "unilateral breathing."

Fluoroscopy

Upon fluoroscopy the differential movement of the chest wall was very apparent. The hemidiaphragms were apparently not under any direct control. In no case was any difference noted between the movements of the right and left leaves of the diaphragm, regardless of the efforts of the patient to control his respiratory movements. Judging from the appearance of the lungs, and particularly the lower lobes (in which the markings and their movements are usually easily seen), there was no difference in aeration or in expansion regardless of the efforts made by the patient to achieve "uni-

lateral breathing." The mediastinum usually swung over to the more vigorously expanding side. This movement was only slight and no measurements were made, but this phenomenon was repeatedly observed by several unprejudiced observers.

Bronchospirometry

This was performed on eight patients who were to receive thoracoplasty or pulmonary resection. The usual bronchospirometry with Zavod catheter was performed and tracings were secured, usually for a five minute period. The patient was then asked to "breathe unilaterally." It has been suggested that, because of the sedation plus the catheterization, the ability to breathe differentially might be lost. Therefore, in each case, before tracings were secured, two physicians and a nurse attempted to evaluate the patient's ability to control his breathing. In no instance were tracings made until all three could see a definite moderate or marked difference between the two sides. After the tracings were made, usually for a two minute period, the

Table II

	Bilateral Breathing Tidal Air		Dextrolateral Breathing Tidal Air		Sinistrolateral Breathing Tidal Air		Oxygen Consumption Bilateral Breathing	
	R	L	R	L	R	L	R	L
Case 1	52%	48%	53%	47%	52%	48%	48%	52%
Case 2	51	49	—	—	50	50	27	73
Case 3	53	47	52	48	—	—	57	43
Case 4	48	52	—	—	47	53	33	67
Case 5	42	58	39	61	38	62	24	76
Case 6	42	58	37	63	38	62	44	56
Case 7	47	53	48	52	47	53	37	63
Case 8	56	44	—	—	54	46	32	68

tidal air was measured on each side. This was done by measuring with calipers the height of each respiration on each side for the two minute interval, as recorded on the revolving drum. These readings were then compared with the tidal air as recorded in a similar period of time during quiet bilateral breathing. It will be noted that the tidal air, and not the oxygen consumption, was measured for this determination

From these readings it can readily be seen that there is no bronchospirometric evidence of true unilateral breathing. Although the term "tidal air" was used, it is not strictly accurate, inasmuch as it represents a forced effort rather than a quiet respiration. In cases 2, 4, 5, 6, 7 and 8 the tidal air gave a much poorer indication of the true condition of the lungs than did the oxygen consumption. In each of these instances the ventilation equivalent (liters of air breathed for each 100 c.c. of O_2 absorbed) was high, leading to a large air exchange but relatively low oxygen absorption. This was true in each of these instances for the more seriously diseased of the two lungs.

TABLE III

	Pnx Side	Percentage of Collapse at Rest	Percentage of Collapse with Deep Breathing	Percentage of Collapse with Right Unilateral Breathing	Percentage of Collapse with Left Unilateral Breathing
Case 1	R	30	20	20	20
Case 2	L	30	20	20	20
Case 3	R	35	15	20	20

Four of the patients were able to immobilize either the diseased or the normal side. In these instances readings were obtained with bilateral right-sided and left-sided breathing. In the other four, immobilization of the chest wall on the side of the disease was satisfactory but these individuals could not immobilize the healthy side and breathe with the chest wall on the involved side. Therefore, in these instances (cases 2, 3, 4 and 8), only the uninvolved side was utilized in attempting to get readings with "unilateral breathing." It must be emphasized, however, that during the broncho-spirometry of these cases both sides of the chest moved freely at first; while the differential readings were being obtained, the diseased side was successfully immobilized by the patient.

PNEUMOTHORAX CASES

Three patients with pneumothorax were studied. All were ambulatory. In no case was there contralateral disease. In each the pneumothorax was free of fluid, adhesions or visible pleural thickening.

FLUOROSCOPY

In addition to the movements of chest wall, diaphragm and mediastinum described above, the partially collapsed lung was visualized and its movements recorded.

TABLE IV

	Side	Quiet Breathing	Deep Breathing "Bilateral"	Right Unilateral Breathing	Left Unilateral Breathing
Case 1	R	−7 −4	−14 −6	−13 −6	−13 −6
Case 1—After 500 c.c. of air		−5 −2	− 9 −2	− 9 −2	− 9 −2
Case 2	L	−6 −2	− 9 −2	− 8 −2	− 8 −2
Case 2—After 450 c.c. of air		−4 0	− 7 +1	− 6 +1	− 5 0
Case 3	R	−5 0	−15 0	− 5 0	− 5 0
Case 3—After 500 c.c. of air		−4 +1	−10 +1	− 4 +1	− 4 +1

As can be seen from these figures, no difference in collapse or expansion was obtained with "unilateral breathing." The percentage of collapse is always less when a deep breath is taken in the presence of pneumothorax, since the volume of the lung increases while the volume of the pneumothorax remains approximately the same. This decrease is reflected in the percentage figures in table 3. However, this decrease is the same whether the deep breathing is bilateral, dextrolateral or sinistrolateral.

Manometry

With the patient supine, the pneumothorax needle was inserted and readings obtained.

These readings bear out the previous observations. There is no evidence of increased negativity with "unilateral" breathing.

Discussion

Respiration is such an automatic and unconscious act that, except for deep breathing exercises, little attention has been given to its voluntary control. It is quite amazing to watch a well-trained patient breathe at will by moving either side of the chest while voluntarily immobilizing the other. In an effort to aid in the rehabilitation of patients with pulmonary, pleural and chest wall diseases and injuries, considerable use is being made of differential unilateral breathing exercises. We could find no reports of respiratory function studies done in conjunction with such exercises.

We have been using these exercises for some months at the Veterans Administration Hospital at Wood. This study was initiated to determine how much effect such exercises have upon the underlying lung. Thus far our studies have led to the conclusion that they have little or no effect upon the ventilation of the lungs. From fluoroscopic examination it would seem that this failure to affect the pulmonary expansion differentially is due to (a) failure to immobilize one leaf of the diaphragm by voluntary control, (b) mediastinal shift, which also equalizes the expansion of the lungs.

Further controlled study is needed before it can be held as demonstrated that such differential breathing is of any actual value. However, we have not studied the question of the effect of these exercises upon the chest wall or early pleural adhesions, and we do not wish to imply that their inefficacy has been proved in this direction.

Summary and Conclusions

1. Eleven patients have been trained to perform "unilateral breathing."
2. All have been studied by observation and fluoroscopy.

3. In addition, eight have had bronchospirometry and three have had manometric pressure readings with a pneumothorax needle in situ.

4. These studies have led us to the conclusion that, despite the marked difference in chest wall movements, the lungs ventilate about the same during "unilateral" as during bilateral respiration.

ACKNOWLEDGMENT

Dr. Francis B. Landis rendered great assistance in the performing of the bronchospirometric studies.

Miss Jean Allen, R.P.T., assisted in training some of these patients to perform the breathing exercises.

TREATMENT OF CHRONIC CONGESTIVE CARDIAC FAILURE WITH ION EXCHANGE RESINS*

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In recent years, studies of heart failure have stressed the fact that, when cardiac output is inadequate for tissue needs, the body compensates by increasing the blood volume and the tissue fluid volume. Since in most cases kidney function is reasonably good, tubular absorption of sodium is complete and retention occurs. The problem of increasing the excretion of sodium has therefore become of primary importance in the clinical treatment of congestive failure. Together with digitalization, salts such as ammonium chloride, mercurial diuretics and strict low sodium diets have become the mainstay of treatment. In addition, salt restriction with or without mercurial diuretics has been found valuable in the treatment of hypertension and may be the basis for the favorable effects of the so-called rice diet. In spite of strict adherence to these measures, a certain proportion of cases fail to respond.

A new therapeutic approach to the edematous states involves the use of cation exchange resins by means of which exogenous sodium can be removed by the intestinal tract, and absorption into the body prevented. This paper deals with a small series of cases in whom such a resin was tried clinically. We selected only cases which over a period of time had failed to show sustained improvement on ordinary measures for the treatment of congestive failure, in that they continued to have edema even with free use of mercurials, with rigid salt restriction and full digitalization, or those who had free fluid requiring repeated taps and who were not appreciably helped by injections.

Case Reports

Case 1. A 50 year old housewife had a chronic rheumatic heart with mitral and tricuspid disease. In 1946 she was hospitalized because of peripheral edema and ascites. During the years 1946 and 1947 she required an abdominal paracentesis at intervals of six weeks to two months, and during the year 1948 as frequently as every two to three weeks. When first seen by one of us in January, 1949, the patient had auricular fibrillation and was in advanced congestive heart failure. She had not been recently digitalized. Significant findings on examination were: a severe edema of both lower limbs which extended to the thighs, a marked ascites, a large pulsating and tender liver, and evidence of a right pleural effusion. She was digitalized, put on a low sodium diet, and given ammonium chloride and mercuhydrin orally rather than parenterally, because she objected to injections. Under this régime she showed some improvement but lived as an invalid with constant edema and ascites, requiring paracentesis every three weeks. Six months later, during September and October of 1949, it became necessary to increase the frequency of the

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abdominal taps to every two weeks and occasionally to every 10 days. She now consented to intravenous injections of mercuhydrin once a week, which helped decrease the need for abdominal paracentesis to the previous interval of three weeks. On March 23, 1949, an abdominal paracentesis was done and the patient was started on carboxylic resin in dosage of two heaping teaspoonfuls three times daily after meals.

After taking the resin for two weeks there was little change in the patient's weight. However, she offered the information that she felt "lighter" and had less pressure in the abdomen. An abdominal tap was not necessary until four weeks after resin had been started. The amount of fluid removed was approximately 500 c.c. less than usual. Previously the patient had gained 10 pounds between taps; during these first four weeks she lost 16 pounds in weight. The next abdominal paracentesis was not required until five weeks later, and it yielded 1,000 c.c. less than usual. This was the longest interval she had had without an abdominal paracentesis

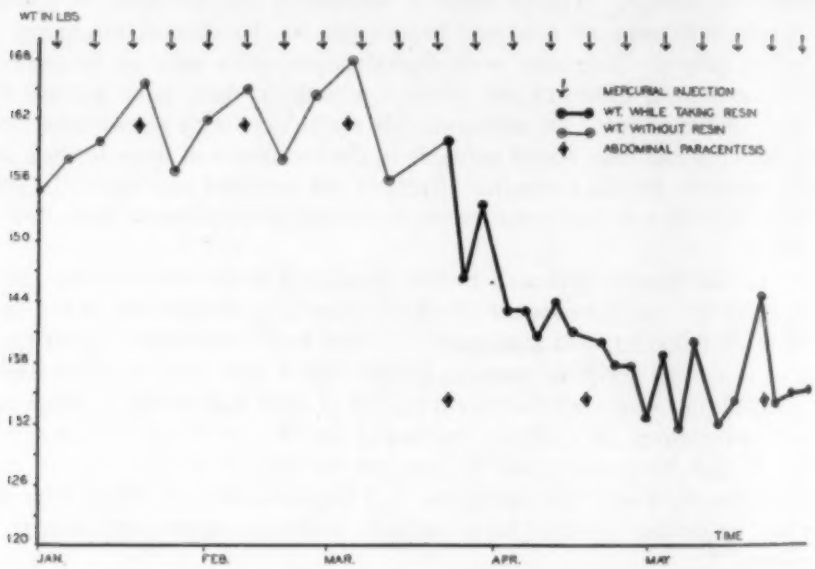

FIG. 1. *Case 1.* A 50 year old patient with chronic rheumatic heart disease and chronic congestive failure of approximately four years' duration. Carboxylic resin started two months ago.

in two and one-half years. More striking than the weight loss and the decreased need for abdominal paracentesis has been her subjective improvement. She is less easily fatigued and dyspneic. Her appetite as well as her mental outlook is much improved (see figure 1).

Case 2. A 60 year old housewife, a known hypertensive for 10 years, began to complain of exertional dyspnea and ankle edema seven years ago. In 1949, following an episode of severe chest pain for which she sought no medical attention, she complained of increasing exertional dyspnea and edema. Two years ago she was digitalized for congestive heart failure. When first seen by one of us in April, 1949, she was in advanced congestive heart failure with pulmonary edema. Along with digitalis, which the patient was taking in maintenance doses, she was given ammonium chloride, aminophylline and injections of mercuhydrin at three day intervals, together with a low sodium diet. Improvement was gradual and at the end of six months the

patient required 2 c.c. of mercuhydrin at five day intervals to keep her edema free. Her activities were limited to light housework. On February 16, 1949, the patient was started on carboxylic resin in dosage of two heaping teaspoonfuls three times daily after meals.

Here again there was no appreciable weight loss after taking the resin for two weeks but the patient commented upon how much "lighter" and stronger she felt. In six weeks after taking the resin she lost 10 pounds in weight, and mercurial injections were decreased to every two weeks. She has been maintained with only occasional edema and with continued weight loss. A striking feature of her subjective improvement has been her ability to increase her physical activities with comfort (see figure 2).

Case 3. A 57 year old machinist had been a known hypertensive for 10 years. In January, 1948, he was admitted to the Princeton Hospital in congestive heart failure. When discharged three weeks later he was edema free. No ascites or liver enlargement was noted on this admission.

FIG. 2. *Case 2.* A 60 year old patient with known hypertension for 10 years and congestive heart failure for seven years. Carboxylic resin started three and one-half months ago.

From January, 1948, to October, 1949, the patient was maintained on 1.5 gr. of digitalis daily. In September, 1949, he was hospitalized in Middlesex General Hospital because of increasing peripheral edema and ascites. Under a régime of bed rest, continued digitalis, ammonium chloride, salt restriction and 2 c.c. doses of mercuhydrin given at three day intervals, the patient improved. He was discharged from the hospital six days later without peripheral edema, but his liver edge was palpable three fingerbreadths below the costal margin and there was evidence of a small quantity of free fluid in his abdomen. Three weeks later he was readmitted, again with increasing edema and marked ascites. He was maintained on a régime similar to the one described above. However, despite abdominal paracentesis and injections of 2 c.c. of mercuhydrin at three day intervals, there was little clinical improvement over a period of three weeks. He continued to complain of fatigue,

anorexia and orthopnea, and a severe ascites remained. At this time, December 18, 1949, the patient was started on carboxylic resin. He was given two heaping teaspoonfuls three times a day, along with a maintenance dose of digitalis, ammonium chloride and injections of 2 c.c. of mercuhydrin every three days.

After he had taken the resin for two weeks there was no appreciable difference in his weight but, as in the previous cases, he noted that his appetite had improved and that he had less indigestion and pressure in his abdomen and chest. By the third week he had lost 10 pounds in weight and there was a noticeable decrease in his ascites. At this time, due to the patient's negligence, carboxylic resin was omitted for 10 days, with the result that he regained 10 pounds. However, within two weeks after the resin was resumed he lost 25 pounds in weight and was free of peripheral edema and ascites. Along with this remarkable clinical improvement, there was an equal subjective improvement. The patient had an excellent appetite, felt very much stronger and began to consider employment. For the next three

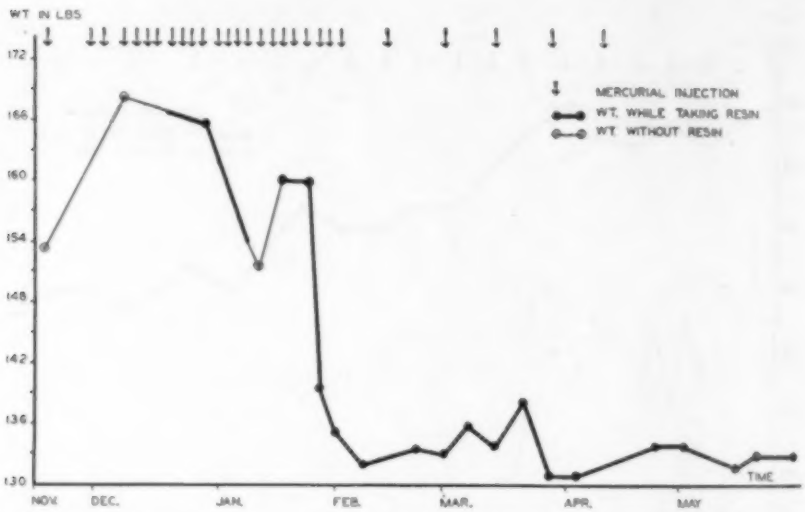

FIG. 3. *Case 3.* A 57 year old hypertensive patient with known congestive heart failure for approximately two and one-half years and known ascites for nine months. Carboxylic resin started six months ago.

months he maintained a constant weight, with mercurial diuretics given only at two week intervals. The resin dosage was continued but was given only four days in seven. Although no signs of potassium deficiency were noted, 10 drops of potassium iodide were administered three times daily for the rest of each week. For the last six weeks he has required no mercurial diuretic. Because of the length of time this patient had been taking the resin, determinations of blood calcium, non-protein-nitrogen and carbon dioxide combining power were recently done, with normal results.

Four other cases presenting similar clinical problems were started on the resin in the past six months. In one of them the drug was reported by the patient as causing intolerable burning in the stomach. The addition of amphojel and a trial in milk and in mashed potatoes gave no better results. The drug was therefore omitted and the patient's condition is

steadily deteriorating. In the second and third cases the resin was used for about two weeks but at the end of this period both patients refused to continue because of repugnance to the dose, though it caused no definite gastrointestinal discomfort. Neither patient showed any change in weight during the two-week trial period. Both patients show advancing edema and a downward course. The fourth case (Mrs. M. G.) had had arteriosclerotic heart disease with congestive failure for at least two years. It was complicated by repeated right pleural effusion, requiring thoracentesis at intervals of three to four days. She tolerated the resin well and took the full dose for six weeks. In this time she improved in that her weight was lower, and the taps were reduced to seven to eight day intervals. However, her general condition was poor, she was severely diabetic and she died suddenly soon after leaving the hospital. It is therefore impossible to evaluate the therapeutic response of this patient.

Ion exchangers have been used in industry for many years. Natural earths of similar properties have been recognized since antiquity and in ancient Greece were famous as antidotes for various poisons. Although their physicochemical properties were not understood, they were valued during the Middle Ages for the same purpose, and much superstition and mystery became associated with their use. In 1946 Dock [1] first suggested the medical use of a cation exchange resin for producing sodium depletion of the ingested foods.

These ion exchangers are relatively insoluble substances which have the unique property of releasing one ion and replacing it with another. Sodium or calcium resins, for example, will take up hydrogen ions in the stomach and thus reduce gastric acidity, as in peptic ulcer therapy. Acid resins, on the other hand, will act in the intestinal tract to take up sodium, calcium or potassium and release hydrogen. While resins materially cut down the absorption of sodium in the intestinal tract, they do not influence the normal absorption of phosphates, chlorides or sulfates. For this reason a compensatory acidosis is produced, with fall in the carbon dioxide combining power, rise in chlorides but constant pH of the blood. This action of resin feeding is therefore similar to the administration of ammonium chloride. The electrolyte pattern in the urine is likewise changed during the period of resin ingestion. The kidneys balance the excess phosphates, chlorides and sulfates by the formation of ammonia to compensate for the lower amount of calcium, potassium and sodium excreted through this channel.

In two cases of congestive failure and one of cirrhosis of the liver treated in 1949 by Irwin and his associates,[2] all showed complete loss of edema, reduction in sodium excretion in the urine, and increase in fecal excretion of this salt. They found that, in vitro, ions of higher valence or molecular weight will be bound by the resin in preference to ions of lower valence; therefore, potassium or sodium will be chosen in preference to calcium However, since the amount of sodium in the gut is much greater than

either calcium or potassium, a large proportion of the ingested resin is available for binding sodium, and in vivo studies gave better results than anticipated from the test tube.

Danowski [3] also confirmed the action of the carboxylic exchange resin in studies done on dogs and humans during periods of measured diets. He reported prompt diuresis of edema when it was used in conjunction with low sodium regimen, and noted the development of acidosis with overbreathing in one case with renal failure. There was a significant increase also in potassium loss in the stool associated with losses in body potassium and slight decrease in serum potassium concentration.

McChesney and McAuliffe [4] studied a number of ion exchangers to determine their relative efficiency from the standpoint of binding the largest amounts of sodium with the least possible amounts of calcium and potassium. They found very little difference in results in the various resins in a 21 day experiment on rats. They also noted, however, that when resins were in the hydrogen cycle, such as the one used by us, the hydrogen ions released in the exchange reaction favored the solution of the relatively insoluble calcium salt and increased their availability for absorption in the body.

The cation exchanger used in this study is a carboxylic resin * in the hydrogen cycle. It is a very fine whitish powder of a sandy consistency and without any unpleasant odor or taste. It has the property, as do other resins of this type, of being an almost completely insoluble substance. It was administered three times daily in a dose of two heaping teaspoonfuls, stirred up in water and drunk immediately, before settling. Where the liquid form was refused, it was also tried in one case each in ice cream or in mashed potatoes. All cases which continued to use the resin found the administration in water most easily tolerated. The addition of antacids between meals did not seem to furnish any particular comfort to those patients who complained of symptoms from the drug. Where good results were obtained and the patient became symptom-free and edema-free, the doses were omitted for a portion of each week, the daily dose remaining the same. The patients were asked to adhere to moderate salt restriction in the diet. In other words, they were allowed ordinary milk (valuable particularly since the question of calcium depletion has been raised in the use of an ion exchange resin) and used bakery bread, ordinary butter, etc., but avoided salty foods and the use of the shaker.

Since the mechanism of action of the resin is to prevent absorption of sodium into the body, rather than to remove the excessive tissue sodium from the already "brine-logged" patient, it is necessary to use the medication for prolonged periods and, in addition, to continue at least for a time the other therapeutic agents for promoting excretion of sodium, namely, the diuretics.

* Material furnished through the courtesy of the National Drug Company of Philadelphia, Pennsylvania.

These resins present certain advantages as therapeutic agents. One is the fact that they allow a patient to eat a more normal diet, free from the monotony of extreme sodium restriction. In the average home, where food is prepared for a family unit, it is difficult to achieve a really low sodium diet. To be truly minimal in sodium content, a diet would have to exclude all root vegetables, all leafy vegetables, all milk (except dialyzed milk), all meat, and eggs. In diseases such as cirrhosis of the liver with hepatic decompensation, where a high protein diet is desirable as well as one low in salt, the resins make such a diet possible.

Another advantage is that in cases responding to the resin, mercurial diuretics can be spaced more widely, thus cutting down the number of injections. It avoids the necessity for further impairing a normal function (tubular reabsorption) by the toxic effects of mercury. By presenting less sodium to the kidney for excretion, the subject's diminished but by no means absent capacity to excrete this salt is preserved.

Fortunately, the resins appear to be relatively nontoxic in the doses used. There is one exception, namely, where a patient has marked impairment in renal function, with inability to form ammonia. In such a case the compensatory mechanism cannot go into action, and severe acidosis may result. The question of depletion of the mineral substances—potassium, calcium and even magnesium, iron, manganese, copper, cobalt and amino acids—has been raised with prolonged use of the resin. However, no clinical evidence of such deficiency has thus far been encountered. We have tried to prevent such a condition in the case of calcium by using more liberal milk ration, and of potassium by giving potassium iodide or some other potassium salt. The chief drawback in the use of the resin is its relatively large bulk, so that its acceptability as a therapeutic agent is somewhat variable. Many patients have difficulty in swallowing a large amount of fluid containing material in suspension. Capsules would present just as great a problem because of the large number required to obtain sufficient absorption of sodium to be effective. The resin was therapeutically accepted in only about half the cases offered its use.

Discussion

So limited a number of patients is not sufficient to establish the clinical value of the ion exchange resin. However, the observations on these gravely ill patients are encouraging and warrant further studies. This form of treatment appears to be particularly indicated in the following types of cases:

1. So-called "irreversible" congestive failure—no longer responsive to orthodox drugs.
2. Patients who have recurrent free fluid in pleural or abdominal cavities.
3. Patients who, because of their home conditions or because of restaurant meals, are unable to adhere to a truly low sodium diet.

It may also be worth a trial in the severely hypertensive who is psychologically unfitted for or physically unable to obtain a low sodium diet, and in the cirrhotic patient with hepatic failure and edema.

Summary and Conclusions

1. The authors present a preliminary report on the use of ion exchange (carboxylic) resin in patients with chronic edema of cardiac origin.

2. Its use entails the prolonged daily ingestion of relatively large quantities of an insoluble powder.

3. Patients able to take the drug showed some improvement, dramatic in at least one case.

4. Results are sufficiently encouraging in patients with "intractable" cardiac failure to merit further study of these patients and of others like them.

Addendum

Since this paper was submitted for publication the composition of the resin has been changed to a powder of a finer consistency which contains 20 per cent in the potassium cycle and 80 per cent in the hydrogen cycle. Its effectiveness appears somewhat greater and its palatability has been much improved.

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ACUTE PORPHYRIA *

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The purpose of this paper is to review the recent literature of acute porphyria and to present four additional cases. It is hoped that this will stimulate more interest in the subject, in order that the diagnosis may be made early and treatment instituted promptly with the expectation of improving the prognosis.

Definition

Acute porphyria is a disease of disturbed pigment metabolism, constitutional or toxic, characterized by abdominal pain, nervous and mental symptoms, and the excretion of large amounts of porphyrins in the urine. It is stated to be a familial disease, usually inherited as a Mendelian dominant characteristic; and to be more common in women.

Biochemical Considerations

Porphyrins are pigments occurring in plant and animal life. Actioporphyrin is the pigment basis of chlorophyll in plants. Protoporphyrin is the porphyrin of blood pigment. Protoporphyrin combines with iron and globin to form the basis of hemoglobin.

The common chemical structure of all porphyrins is four pyrrole rings bound by four additional carbon atoms. The two porphyrins important in the cases of porphyria are: (1) coproporphyrin, which occurs in normal feces, and (2) uroporphyrin, which is found in small quantities in normal urine.

Under unknown circumstances, uroporphyrin and coproporphyrin are produced in excess and excreted in the urine and feces.

The identification and differentiation of uroporphyrin and coproporphyrin and the various types and isomers are didactically significant. Inasmuch as they are still under investigation, we can do no better than to refer to the excellent paper of Watson and Larson.[30]

These authors state that the exact site and mode of formation of coproporphyrin and uroporphyrin remain in doubt. It is thought that the liver is the most important organ of excretion of porphyrins.

The excessive excretion of the type III isomers of the porphyrins is considered pathologic in acute porphyria. This may be in amounts sufficient to color the urine from red to almost black. It may be present as a colorless chromogen, porphobilinogen, which is changed to coprobilinogen by sunlight or by an oxidizing agent, such as potassium permanganate.

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History

In 1841, Sherer described a red pigment formed by the action of a strong sulfuric acid on hemoglobin. In 1871, Hoppe Seyler first revealed the chemical and physical properties of this pigment and named it hematoporphyrin. In 1911, Gunther defined it as an error of pigment metabolism and described it as a clinical entity. Fisher, in 1924, first isolated coproporphyrin and uroporphyrin in the urine of patients with acute porphyria.

Types of Acute Porphyria

No attempt is being made in this paper to discuss any type of porphyria other than the acute form. This necessarily precludes the discussion of the congenital and the chronic types.

Two forms of acute porphyria are recognized, the idiopathic and the toxic. The former is constitutional or endogenous, and the latter, due to metals or chemicals, is exogenous.

Incidence

Up to 1939 some 250 cases of acute porphyria had been reported. Since 1939, many additional cases have been noted in the literature. This is particularly true since 1944, at which time Nesbit [7] reviewed the subject. Acute porphyria is more common in women than in men in the ratio of 4:1. The literature furnishes no information regarding the incidence in colored and white. The disease is more common in the third to the fifth decades. Waldenstrom listed 17 Swedish families with more than one case, which indicates a strong familial tendency.

Etiology

The idiopathic type is considered to be due to a constitutional defect resulting from an inborn error of pigment metabolism. The exact exciting agent is not known. The toxic form results from metals and drugs, and occurs in certain diseases. Of the heavy metals, lead and arsenic are the common offenders. Drugs implicated include the barbiturates, nitrobenzol compounds and the sulfonamide group.[1]

Toxicology

The injection of hematoporphyrin into experimental animals has a definite effect upon the circulation, particularly the cutaneous circulation, resulting in a gradual increase in blood pressure beyond the normal. This is followed by a fall in blood pressure, with collapse and death. In humans it has been observed that the injection of hematoporphyrin hydrochloride (Photodyne), used in the treatment of depressive psychoses, may result in a severe peripheral neuritis. The nerves lose their myelin sheaths and the anterior horn cells show degenerative changes.

Symptoms

The typical case of acute idiopathic porphyria is characterized by the triad: (1) acute abdominal pain; (2) neuritic pains, and (3) the voiding of red urine.

The acute abdominal pain is severe and colicky, and associated, as a rule, with constipation and vomiting.[3] It strongly resembles that of gall stone colic and has often been mistaken for it. It is not unusual to find scars on the abdomens of the patients with acute porphyria, for many have been opened on the presumptive diagnosis of an acute abdomen.

The neuritic pains radiate chiefly across the lower abdomen, but they also shoot down the legs. Foot and wrist drop have been observed, and not infrequently this proceeds to a symmetrical progressive ascending paralysis with death from respiratory failure. Sensory disturbances are rare. Varied types of psychic disturbances have been seen. The label of psychoneurosis has been pinned on many before the investigation for porphyria was started.

The urine may be red upon voiding or become red on exposure to light. It has the classical port wine appearance and can hardly be mistaken. At times the urine is more icteric, and only after laboratory examination is the diagnosis of porphyria confirmed.

The cardiovascular manifestations include tachycardia and T wave changes in the electrocardiogram.[5] Hypertension, paroxysmal in type, is not uncommon in the acute attacks, diastolic pressures as high as 140 having been recorded. Jaundice is a complication frequently present in the later course of the disease.

Laboratory

The entire clinical picture so simulates an acute abdomen, or disease of the central nervous system, that without laboratory confirmation a diagnosis of porphyrinuria cannot be made.

There are four ways of identifying prophyrins in the urine:

1. Spectroscopic examination.
2. The Watson Schwartz test. Erhlich's aldehyde is added to the urine, followed by the addition of chloroform. This is shaken and a characteristic red color appears.
3. The methyl esters of porphyrins have a characteristic melting point after crystallization from urine.
4. Exposure of the urine to ultra-violet light will result in a characteristic pink color.

Leukocytosis is the rule during the acute attacks. This adds to the confusion in differentiating porphyria from the acute abdomen. Spinal fluid examination is of assistance only in ruling out other conditions of the central nervous system.

Pathology and Pathologic Physiology

A degenerative process of the peripheral nerves and in the anterior horn cells has been commonly described, an outstanding feature being a patchy degeneration of the myelin sheath. Changes have been noted in the cells of the sympathetic ganglia and include pigmentation, chromatolytic changes, and nuclear and intracapsular vacuolization with localized round cell accumulation. More pronounced changes have been described which are essentially cytolytic. The cortical cells show decided pyknosis and, in some instances, vacuolization of nuclei. Many show no chromatin material and no nucleolus. Masses of amorphous pigment are seen in all sections and include both iron-containing and non-iron-containing pigment. The motor cells of the anterior horn of the spinal cord and, to a lesser extent, the posterior horn at all levels show apparent pyknosis and shrinking, and various types of pigment are observed. The Purkinje cells of the cerebellum show definite signs of degeneration. The liver is enlarged, and cloudy swelling to necrosis has been noted. Increased brownish yellow pigment in the hepatic cells and Kupffer cells is present, and these cells may be enormously enlarged. Their cytoplasm contains iron and iron-free pigment. The spleen may be enlarged and show proliferation of the reticulum cells. Fibrinoid changes in the reticulum cells of the Malpighian bodies have also been noted. Large amorphous masses of brown pigment extracellularly, as well as within the macrophages, may be seen in the sinusoids, and throughout the red pulp. The kidneys reveal occasional nests of pigment granules, mostly in the free endothelial cells of the glomerular capillaries and in the cytoplasm of the tubular epithelial cells. Diffuse cloudy swelling of the epithelium of the tubules is observed. The bone marrow is hypoplastic and contains large cells laden with brown pigment. Considerable muscular atrophy may be present. The myocardium may show degenerative changes and hemorrhages.[3, 7]

The relation of the defects in porphyrin metabolism to symptomatology and pathology is not clear. A direct application of the porphyrins to the bowel produces spasm unrelieved by atropine. The abdominal symptoms in patients gradually subside while porphyrins continue to be excreted in the urine. It is felt that degenerative changes in the autonomic ganglia, particularly the celiac ganglia, are a possible explanation of the abdominal symptoms. Intracellular pigment deposits and hepatic cirrhosis may account for jaundice, which is occasionally present.[3]

The convulsions observed may possibly result from spasm of blood vessels. The pressor episode—that is, the episode characterized by increased blood pressure, a sensation of cold, and an increased pulse rate—is probably a result of the extreme capillary spasm observed in the skin. With the capillary microscope, injury to capillaries in the form of aneurysmal dilatation has been noted. Waldenstrom described changes in the arterioles as

subacute inflammatory reactions with some necrosis and sclerosis. Pains in the joints may possibly be due to capillary spasm and microscopic hemorrhages.

Experimentally, a noticeable disturbance in gastric contractility has been observed. With a balloon in the stomach a prolonged period of atony was noted, interrupted only by an occasional rush of reverse peristalsis. There was absence of peristaltic sounds over the abdomen. Immediately after injection of neostigmine solution, the resumption of gastric contractions was noted. The injection of a combination of neostigmine and mecholyl resulted in a pronounced reaction, with definite capillary dilatation and gastric intestinal contraction. Symptomatic relief was then observed.

Differential Diagnosis

Acute porphyria must be differentiated from acute gastrointestinal episodes, acute neurologic and psychiatric diseases, and from miscellaneous conditions causing red urine. The abdominal colic and vomiting so simulate those of acute intestinal episodes that surgery has often been performed unnecessarily. This poses a difficult problem until porphyrins are isolated in the urine.

Diseases of the nervous system which are confused with acute porphyria are Guillain-Barré syndrome, Landry's paralysis, tick paralysis, poliomyelitis, etc. The spinal fluid findings as well as the history are helpful, but, again, the presence or absence of porphyrins is the deciding feature.

There are many miscellaneous conditions causing a red urine. Patients taking pyridium or eating red beets may have a pink color in the urine. This may be similarly noted in the alkaline urine of patients taking phenolphthalein, rhubarb, senna, cascara, or santonin. Hematuria or hemoglobinuria and myoglobinuria are endogenous causes of red urine.

Treatment

Inasmuch as the cause of this disorder is unknown, except for the cases of toxic etiology, there is no specific treatment of value according to the literature. Necessarily, it is important to remove all elements of toxic nature, particularly drugs and heavy metals.

Prognosis

The prognosis is guarded since the mortality rate is high. This is particularly true in cases in which neurologic symptoms are present. In these latter, the rate reaches 80 to 90 per cent. Waldenstrom's series of 100 cases is the largest reported. Of these, 20 died within one year of the appearance of the disease clinically; two lived eight years; of the 12 living at the time he wrote his article, one had survived for 27 years.

Case Reports

Case 1. A 48 year old male was first seen January 14, 1947, at which time he was complaining of constipation, headache, and bleeding from the rectum. His symptoms dated back 15 years: a hemorrhoidectomy was to have been performed in one of the large clinics, but the patient went into shock on the operating table when the inhalation anesthetic was given and nothing was done. Since then he has been very apprehensive about any surgical procedure. However, the bleeding, weakness, and headaches were so constant he was forced to seek attention.

His past history revealed many attacks of typical gall bladder colic, but his anxiety had always prevented surgical intervention. The family history was noteworthy. His father died at 84 of senility; his mother was living and well at 78. One sister had died of pernicious anemia, one brother of encephalitis, and one of diphtheria. Seven other siblings were living and apparently well. On examination in the office, the patient appeared pale, sallow and washed out. Blood pressure was 140 mm. Hg systolic and 80 mm. diastolic. The liver was palpable two and one-half fingerbreadths below the costal margin but was not tender. The rectal examination revealed hemorrhoids to be present, with a moderate prolapse of the rectum. The proctoscopic examination showed no evidence of neoplasia or ulceration.

The blood count taken revealed a 40 per cent hemoglobin, with 2,990,000 red blood cells. He was given several small transfusions in the emergency clinic without any immediate untoward reaction. A barium enema and contrast barium enema were negative. Noted incidentally was a large solitary biliary calculus.

He consented reluctantly to rectal surgery. This was carried out under spinal anesthesia. The postoperative course was uneventful until the eighth day, when he began complaining of cramps in the toes, left calf and thigh. He was told that this was a reaction to the anesthesia, and was discharged from the hospital within a few days. He returned to our office March 14, 1947, on the nineteenth postoperative day, because of frequent attacks of pain in the right upper quadrant. These were interpreted as gall bladder attacks by the patient, who stated that his urine was dark in color. In addition he complained of marked weakness of his extremities and of being unable to raise his arms. His hands were swollen and the grip was poor. A fresh urine was dark, smoky brown in color, and negative for bile by various tests. The Watson-Schwartz test for porphyrins was strongly positive.

He refused to enter the hospital and was treated on an ambulatory basis. This consisted of parenteral liver, and vitamins B and C intravenously. The symptoms increased, with abdominal pain, nausea and vomiting. After a week at home he became worse, manifesting mental instability and insomnia, as well as progression of the weakness. He was unable to walk without help or to shave himself, and was admitted to Touro Infirmary on March 25, 1947.

Physical Examination: Blood pressure was 140 mm. Hg systolic and 80 mm. diastolic; pulse, 96; respirations, 20, and temperature, 99.6° F. The patient appeared well developed and well nourished, with obvious icterus of the sclera and skin. There was definite limitation of motion of the upper and lower extremities due to weakness. A few anterior cervical nodes were palpable. Heart and lungs were clinically negative. Liver was palpable 7 cm. below the right costal margin. There was slight edema of the extremities. Rectal examination was negative. Diminished deep reflexes of the upper and lower extremities were noted. Cranial nerves normal. No sensory changes observed. Patient irritable, restless and uncoöperative.

Laboratory Findings (March 26): Urine: Positive for porphobilinogen, negative for bile and urobilinogen. Hemoglobin 13.8 gm.; red blood cells 4,280,000; white blood cells 8,800, neutrophils 75 per cent, eosinophils 2 per cent, lymphocytes 18 per cent. Cephalin flocculation: two plus in 24 hours. Non-protein nitrogen 33 mg.

per cent, blood sugar 83 mg. per cent. Icterus index 30. Routine agglutinations negative. Serologic test for syphilis negative. Cysts of *E. coli* present in the stool.

Progress in Hospital (March 27): Specimen of the urine allowed to remain in the sunshine turned the typical dark color of porphyrins. Positive spectroscopic test for uroporphyrin III. Temperature, 100° F. Less muscular cramping today. Receiving intramuscular liver extract, and high carbohydrate, high protein, low fat diet. Daily infusion of 5 per cent glucose in distilled water with large doses of vitamins B and C. Oral vitamins, yeast, thiamine, intramuscular choline chloride and methionine by mouth. March 28: Less muscular weakness noted. Liver now only 4 to 5 cm. below the costal margin. April 1: Fever subsiding by lysis. Weakness much less pronounced. Urine still contains large quantity of porphyrins. Prothrombin determination, 77 per cent. April 8: Total serum bilirubin, 4.5, direct 92 per cent. Icterus index, 35. Marked clinical improvement. Patient now able to shave himself. Minimal weakness of upper and lower extremities. Mentally clear and coöperative. April 10: Liver receding. Total serum proteins, 6.56. Albumin 3.49; globulin, 3.07; cephalin flocculation, 1 plus.

The patient was soon able to walk about his room. Anorexia was marked at times, but there was steady diminution of the jaundice and the porphyrins decreased in amount in the urine. On April 11 he insisted on being discharged from the hospital. Three weeks later he had regained most of his strength and added six pounds to his weight. No clinical or laboratory evidence of jaundice remained. A bromsulphalein liver function test revealed a retention of 30 per cent in 15 minutes, 15 per cent at the end of half an hour, and 0 per cent in an hour. He continued to complain of occasional pains in his right shoulder and in the muscles of his forearms, but there was some muscle weakness at times.

This patient has been followed during the past 18 months and has remained in excellent health. There has been one episode of abdominal pain, which was transitory. The last bromsulphalein, taken September, 1947, showed 20 per cent in 15 minutes and a trace in 30 minutes. He had gained some 24 pounds in weight. At the present time he is actively engaged in his business and spends his weekends hoeing and plowing on his farm.

Case 2. A 58 year old male was admitted to the hospital May 31, 1947, complaining of a severe chest cold and a low grade fever of one week's duration, some generalized weakness, and a feeling of vague abdominal discomfort. The cough was dry and hacking in character, and severe frontal and parietal headache was noted. For the past 24 hours definite chills had been noted. At times the patient complained of retrosternal tightness and pain in the back of his chest. There had been no recent weight loss. *Review of Systems: Eyes, Ears, Nose and Throat:* Mild sore throat. *Gastrointestinal:* No nausea, vomiting or diarrhea. *Cardio-respiratory:* Noted above. *Genito-urinary:* Recent difficulty starting the stream of urine; also, some loss of voluntary control of the urine. *Neuromuscular:* Weakness and severe frontal headache, as above. *Past History:* Patient stated that he had always been in good health, except for the usual childhood diseases. *Social History:* Denied excessive use of alcohol or drugs. Occupation limited to office work. *Family History:* Noncontributory.

Physical Examination: Temperature, 100° F.; pulse, 92; respirations, 20; blood pressure, 150 mm. Hg systolic and 88 mm. diastolic. Patient was a well developed and well nourished white male, approximately 55 years of age who appeared acutely ill. No generalized adenopathy was noted. The exposed areas of skin, especially the face, appeared unusually reddened. Pharynx was negative. The sclerae were suggestive of mild jaundice. Neck: negative. Heart: Sinus rhythm, rate 92, no murmurs. Lungs: Dullness at the right base on percussion, bronchovesicular breath sounds, subcrepitant râles over this area. Abdomen: Slight gaseous distention, but

no tenderness or rigidity present. No palpable organs. Extremities: Varicosities noted both lower extremities. Reflexes: Physiologic. Rectal: Revealed a benign moderate hypertrophy of the prostate.

Progress Record: Laboratory findings on admission: hemoglobin, 13.8 gm.; red blood cells, 4,460,000; white blood cells, 14,050; neutrophils, 74; lymphocytes, 25; monocytes, 1. Stool: unsatisfactory due to excessive oil. Phenolsulfalein, 70 per cent at end of two hours, 40 per cent at end of an hour. Serology: negative. Non-protein nitrogen, 33; dextrose, 91. Urine: acid and rather dark amber in color. Otherwise negative except for an occasional red blood cell and white blood cell. X-ray of chest: Shows the heart diameter and contour to be within normal limits. Minimal diffuse dilatation of the thoracic aorta is commensurate with the patient's age. Calcium deposition is present in the right paratracheal and hilus nodes, the hilus shadows revealing no other abnormality. The lung fields are otherwise clear, and the diaphragms are smooth and well rounded.

May 31: Venous pressure 114 mm. initial, 174 on liver pressure and returned to 100. Temperature up to 101° F. No apparent reason for febrile course. June 1 to June 5: Catheter had to be inserted and retained in situ due to difficulty in urination. Catheterized urine showed a few pus cells and gram-negative bacilli. Septic fever curve continues. In view of pulmonary findings, mild urinary infection, and the leukocytosis, patient was given penicillin, 50,000 units every three hours, with a quarter gram of streptomycin. He also received parenteral liver and vitamins. Blood count June 5: white blood cells, 18,400, with 81 polys. Prothrombin time, 57 per cent of normal. June 6: Urine: very dark port-wine color, positive for large amounts of porphobilinogen, otherwise normal. Patient complained of marked weakness and vague abdominal pain. Seemed restless and at times disoriented. Icterus index 8. Non-protein nitrogen, 31; sugar, 111. Stool culture negative for pathogens as well as parasites. June 6–June 10: No essential change in condition of patient. Fever appeared to be gradually subsiding by lysis, with extremes of 99.6° to 100.8°. Reëxamination of the chest by roentgen-ray revealed no active pulmonary disease. Porphyrins continued to be present in the urine in pathologic amounts. Blood culture was negative on two occasions. White blood cells, 14,250; polys, 81; no eosinophils.

June 12: Cysts and trophozoites of *Endamoeba histolytica* found in the stool. Emetine and diodoquin started. Sedimentation rate, 105 mm. (Westergren). Non-protein nitrogen, 33; chlorides, 443, Co_2 44. Icterus index, 12. X-Ray: A lateral projection of the chest suggests that the diaphragm is normal in contour and position. The angles are clear, and nothing that would suggest the presence of a free subphrenic abscess or a hepatic abscess is present. The right kidney is seen in part and is probably normal in size, contour and position. The left renal outline is not clearly defined. The psoas borders are sharp. Numerous small shadows of calcium density in the left hypochondrium are attributed to calcified tubercles or phleboliths in the spleen. A triangular shadow of calcium density in the left renal region is thought to be extrarenal.

June 14: Afebrile today. Has started hiccoughing constantly. Some tenderness in the right upper quadrant of the abdomen. Lungs now clear to auscultation. Catheter still in situ and attempts at removal result in acute retention. Porphyrins decreasing in amounts in the urine. Receiving daily large doses of vitamins B and C, as well as liver extract by needle. Patient says he feels much stronger, and he appears alert and interested in progress. June 14–June 18: Hiccoughs gradually subsiding. No more fever. Urine no longer has port wine color, but still gives positive test for porphyrins. Laboratory Reports: Cephalin flocculation test 1 plus in 24 hours, galactose tolerance: 22 mg. in half hour and 60 mg. in an hour. Bromsulphalein: 10 per cent retention at the end of 30 minutes.

June 20: Catheter removed and no urinary difficulty noted. Several stool

specimens negative for ameba or other parasites. June 22: Doing very well. Only traces of porphyrins present in the urine samples collected at various times of the day. June 22–June 27: Continues to improve. All antibiotics stopped. A total of 13,000,000 units of penicillin given and 21 gm. of streptomycin. Emetine 10 gr. and diodoquin 100 tablets given. Discharged from the hospital June 27, 1947. Follow-up during the next two months failed to reveal any return of porphyrins in the urine. The patient gained weight and returned to work. Six months following discharge, he reported he was feeling in the best of health and had had no recurrence of symptoms.

Case 3. A 35 year old white male was first seen on September 2, 1947, with the chief complaint of dark urine. For several months the patient stated that he had not felt up to par. There was a noticeable lack of pep and energy, and he tired after slight exertion. The muscles of the neck were painful. His leg muscles felt tired and there was noticeable discomfort after a minimal amount of exercise. Abdominal cramps had been prominent the past several weeks. His appetite had diminished and the bowels were constipated. He also had vague digestive disturbances after eating almost any type of food. For these symptoms he had consulted his physician, who had found chronically diseased tonsils and advised their removal.

Before resorting to surgery he reported for routine physical examination and urinalysis. At this time the urine was found to be very dark. A presumptive diagnosis of jaundice was made and he was referred for treatment. *Review of Systems:* Essentially negative except for marked nervousness with associated palpitation and dyspnea. There was a loss of four pounds in weight. *Past History:* Pneumonia as a child. Pilonidal cyst excised and hemorrhoidectomy four years earlier, without any complication. *Social History:* There was no history of the use of any drugs; his occupation was that of a clothing salesman. *Family History:* Noncontributory.

Physical Examination: Temperature, 98.6° F.; pulse, 80; respirations, 16; blood pressure, 110 mm. Hg systolic and 70 mm. diastolic. Skin: questionable jaundice. Head: Eyes: slight icteric tint. Tonsils chronically hypertrophied and diseased. Heart and lungs clinically negative. Abdomen: no palpable organs. Extremities: some weakness of the hands. Reflexes slightly hyperactive.

Laboratory Findings: The urine revealed a faint trace of bile and was strongly positive for porphobilinogen. A diagnosis of acute porphyria was made and the patient was admitted to the hospital for treatment.

Course in Hospital: On admission September 2, 1947, laboratory reported the following: Blood test for syphilis negative. Hemoglobin, 14.5 gm.; red blood cells, 4.21 million; white blood cells, 5,750; polynuclears, 51; eosinophils, 1; lymphocytes, 48. Nonprotein nitrogen, 30; dextrose, 80. Icterus index, 10. Stool negative. Urinalysis: Essentially negative except for porphobilinogen. The physical examination revealed no change except for a liver which was one fingerbreadth below the costal margin. The patient was put on large doses of vitamin B complex and liver extract, given parenterally. After a few days the icterus index reached a maximum of 15, and then rapidly returned to normal. Clinically there was noticeable improvement after several days of therapy. The urine became lighter in color and the porphyrins faded to a faint trace. He was discharged within two weeks, completely relieved of his muscle pains and decidedly less nervous. He was followed over a period of several months, during which time he noticed his urine dark on occasions, but only infrequently was he tired. Vitamin and liver therapy was continued. When last seen in April of 1948 he had no complaints, although he still noted an occasional wine-colored urine.

Case 4. A 34 year old male was admitted to the hospital May 29, 1948, with the chief complaint of weakness of two years' duration. The patient stated that he was an officer in the merchant marine and had noted generalized muscle pains and increas-

ing weakness with periods of exacerbation and remission. On occasions when he was feeling unwell the excretion of dark red urine was noted. On his last trip at sea, of two months' duration, he had been very seasick and consequently had been on something of a deficiency diet. There was also a history of ingestion of excess quantities of alcohol at irregular intervals, but nothing to suggest addiction.

Review of Systems: Cardiorespiratory: some shortness of breath on exertion attributed to lack of exercise. Gastrointestinal intolerance to fat and fried foods. Genito-urinary: excretion of dark urine as above. No frequency, etc. Neuromuscular: very weak, unable to climb steps in the week before admission.

Physical Examination: Temperature, 100° F.; pulse, 88, respirations, 20; blood pressure, 120 mm. Hg systolic and 80 mm. diastolic. General: Appears acutely ill, unable to move about in bed as directed because of weakness; slight icterus is noted. Head: Pupils react normally. Tongue: No evidence of a deficiency state. Neck: Negative. Thorax: Heart: Sinus rhythm, no murmurs. Lungs: Clear to percussion and auscultation. Abdomen: Liver edge palpable on inspiration, slightly tender. Extremities: Negative except for muscular weakness. Rectal: Negative. Reflexes: Diminished superficial and deep reflexes. No disturbance of sensation. No cranial nerve involvement, except for the history of some difficulty in swallowing and closing the eyes at times.

Laboratory Examination (May 30): Urine reveals porphobilinogen in large quantities. Stool: Negative. Blood Chemistry: Nonprotein nitrogen, dextrose, 100; serum bilirubin, 1 minute direct 3.04 mg. Total: 4.36. Thymol turbidity, 0 units. Urine: urobilinogen positive, 1–40; negative, 1–80. Hemoglobin, 13.2 gm.; red blood cells, 3,870,000; white blood cells, 6,950; polys, 66; eosinophils, 3; lymphocytes, 31. Kahn and Kline tests negative. Stool culture negative for pathogens.

Progress in Hospital (June 1): Treatment begun with daily infusions of 5 per cent glucose in distilled water, plus large amounts of vitamins B and C. Parenteral liver extract was given daily, together with oral choline chloride and methionine. A high protein, high carbohydrate, low fat diet was prescribed. June 2–June 5: Gradual improvement in muscle weakness, increasing appetite and clinical improvement. Urine still shows large amounts of porphobilinogen. Spectroscopic examination confirms same. Liver edge still palpable on inspiration, but no longer tender. June 5–June 8: Slight icterus appears to be fading. Patient now able to shave himself and to move about with ease. Low grade fever (99.6° to 100.8°) persists. Serum bilirubin: Total — 1.36, direct — 0.64. Blood smears negative for malaria. Dark field examination of the urine negative for leptospira. On June 8, urine shows for the first time only a faint trace of porphyrins. June 8–June 12: Fever subsiding by lysis to normal on June 12. Marked improvement in muscle strength, especially in the smaller muscle groups. Patient now ambulatory. Appetite normal. Flat plate of the abdomen failed to identify shadow of the gall bladder or any suggestion of a calculus. Discharge from the hospital at own insistence June 15. Urine specimen daily revealed only a trace of porphyrins.

Patient was followed on an ambulatory basis for three months after discharge. He remained well and did not complain of any weakness or muscle pains. Vitamins and liver extract were continued, as well as diet high in protein and carbohydrate. Patient returned to duty with the maritime service but remained on shore duty.

Comments

Except in recent years, little has been written of acute porphyria and its bizarre manifestations. In spite of its similarity to various diseases, little space has been given to it in the standard medical texts. The severity of the

symptoms in many cases justifies a more prominent position in medical literature.

Because of the simplicity of the Watson-Schwartz test, it has become a part of the routine urinalysis in the authors' office laboratory. In two years only a few positive tests have been found, but the recognition of this abnormal finding has enabled us to make a definite diagnosis in an otherwise difficult case. This permitted us to institute immediate treatment, thereby avoiding progression of the disease and effecting clinical remission. Case 4 was a "typical psychoneurotic" and "no good" for a period of two years until the finding of porphyria.

The consistent finding of an elevated serum bilirubin is sufficient evidence that the liver is either the site of origin of the disease or the organ most commonly affected. The presence of a hepatitis with jaundice constitutes a stumbling block which may veil an underlying acute porphyria. In this series of cases the dark urine was out of proportion to the clinical icterus. Case 1 was interesting from the standpoint of previous transfusions received six weeks prior to his acute episode. The neurologic symptoms and the appearance of urinary porphyrins preceded the onset of jaundice by more than a week.

The presence of ameba in the stool of Case 2 would suggest the possibility of amebic hepatitis. In our experience, in neither virus nor amebic hepatitis have we been able to demonstrate porphyrins in the urine. Further study must be carried out in order to justify this conclusion. Case 3 so closely simulated "catarrhal jaundice," or mild infectious hepatitis, that only because porphyrins were considered was correct diagnosis made. In Case 4, jaundice developed several days after hospitalization while under active treatment. In view of this, little significance can be attached to the deficiency state brought on by seasickness and occasional indulgence in alcohol.

The neuropsychiatric symptoms in all of the above cases were particularly noteworthy in that they showed no relationship to the severity of the gastrointestinal manifestations or to the degree of icterus. Peripheral neuritis, cord bladder, irritability, and general muscular weakness were the high lights in our series.

At one time or another the characteristic dark urine made its appearance. It is admitted that not all of the specimens were consistent in this feature.

Additional laboratory examinations in the form of liver function tests and more exact identification of the porphyrins by spectroscopic and chemical methods would have added much to our study. It is to be regretted that for various reasons the above were not always feasible.

Summary

1. The literature of acute porphyria is reviewed and four additional cases are presented, with no deaths.

2. All cases occurred in males, which is contrary to the expected inci-

dence. This is significant in that routine tests were performed in an office laboratory on all patients where the females outnumbered the males.

3. By the administration of large doses of parenteral liver and vitamins, as well as general supportive measures, clinical remissions were obtained for indefinite periods.

4. Early recognition and prompt treatment should materially improve the prognosis. Unexplained abdominal pain and neuropsychiatric findings should suggest the presence of porphyria.

5. The close relationship between hepatitis and porphyria should stimulate more complete clinical and laboratory investigation.

6. Emphasis is placed on the importance of acute porphyria.

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RESPONSES OF THE ABNORMAL ARTERIAL CIRCULATION TO VARIOUS STIMULI, AS STUDIED BY THE USE OF RADIOACTIVE SODIUM. II. INTRAARTERIAL HISTAMINE, PAPAVERINE, AMINOPHYLLINE AND ADRENALINE; SYMPATHECTOMY AND ETAMON; PAIN *

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As reported in a previous paper, radioactive sodium by its introduction into a distant vein and the measurement of its local accumulation in an extremity was utilized to test the efficacy of several drugs commonly used in the treatment of peripheral arterial insufficiency. These included papaverine, 5 per cent solution of sodium chloride, histamine intravenously, and histamine given by intraarterial infusion.[6] We are now presenting observations made in a similar manner on the effects produced on peripheral circulation by the intraarterial introduction of aminophylline, papaverine, histamine and adrenalin, the intravenous introduction of Etamon, and the blocking of the lumbar sympathetic ganglia by procaine. A comparison of the responses produced by histamine intraarterially and sympathetic block gives pertinent information which delimits the site in the vascular system where their effects are mediated. The effect of painful stimuli on the peripheral circulation is recorded.

Methods

The patient is supine and is allowed to remain recumbent for 15 minutes before the test is started. The window of a Geiger counter is placed against the sole of the foot and under the calf alternately for six to eight minutes at a time, while the count is being taken every minute after the injection into the antecubital vein of about 100 microcuries of radiosodium in a sterile solution of physiologic saline. The counter registers the local arrival of the radioactive material in the blood stream, and the graph as plotted from these measurements represents its rate of accumulation in the extremity. A curve thus established when the patient is not undergoing any experimental procedure is called a basic curve. Such curves show little variation from week to week unless obvious clinical changes occur. Subsequent tests are made to investigate the effect of drugs or to follow the course of the patient's disease. The curve depends upon conditions which affect the blood flow of the extremity and, because of the brief period of observation, are little

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affected by diffusion. Since the test is always conducted under essentially the same conditions, a difference is indicative of a change in a segment of the peripheral vascular system, in the absence of systemic derangements. Graphs made over the gastrocnemius muscle are higher than those recorded over the foot. Muscle tissue, because of its greater vascularity, will have more radiosodium passing through. It will be noted that in these graphs there are two phases, a rapid upgrade and then a leveling of the curve. The significance of this becomes apparent if, while a basic curve is being established, samples of blood are collected almost simultaneously from the femoral artery and the femoral vein and their radiosodium content determined and plotted. At first the arterial concentration is high and the venous low, but in time their values equilibrate. When the peripheral circulation is normal this occurs within three minutes. In the presence of obliterative disease, this can be delayed as much as 15 minutes. The arterial inflow through the femoral artery has to meet and bypass the peripheral resistances set up by the blocked segments. As a result of these delays, venous concentration builds up slowly. Its rising values reflect the grade of the upsweep of the radiosodium graph, while the onset of leveling approximates the time when the arterial and venous concentrations of radiosodium equilibrate. If the coefficient of diffusion of sodium in an extremity were known, these A–V counts could be utilized to calculate the rate of blood flow by means of the Fick principle. Since these values would be the only variables in the Fick formula, and because the radiosodium curve also reflects these, both methods give a semi-quantitative estimation of peripheral blood flow.

If radiosodium during its introduction into the vein should accidentally become extravasated, the resultant pain would be severe and the reflex vasospasm which follows would invalidate any study.[6] A recently described method for the measurement of blood flow, which requires the introduction of radiosodium into muscle or other tissue, should be rendered unreliable by the vasospasm which follows extravascular infiltration with radiosodium and its products of decay.[3, 5]

To correlate the radiosodium studies with other objective findings, skin temperatures are observed at intervals during a test. These are recorded with a Constantin wire thermocouple and a Leeds and Northrup potentiometer under average room conditions. Oscillometric readings are also taken at the time of each test, using a Boulitte oscillometer.

Arterial circulation time is measured by injecting 5 to 10 c.c. decholin, 20 per cent into the femoral artery within three seconds and noting the time it took to reach the patient's tongue, and then subtracting the time it took a similar dose to travel from a foot or femoral vein to the tongue. No untoward effects were noted except a burning sensation when given very rapidly. This may be due to leakage around the needle or the hypertonic concentration of the bile salts used.

The method for the arterial infusion of histamine has been described

previously.[7] Lumbar block, when performed, anesthetizes the first, second and third lumbar ganglia.

Results

1. Significance of a Single Series of Geiger Counts or Basic Radiosodium Curves. It has been suggested that by relating the height of a single curve for an individual to that of a group of normals or persons having a known disease, the degree of vascularity and arterial efficiency could be determined.[6, 10] The difference in the heights of the curves in the foot and calf as seen in the various figures of this paper would appear to bear this out. However, that such a curve alone cannot serve as a diagnostic test is made evident by a study of figure 1, which shows a group of low curves obtained at the feet of patients with anxiety states, scleroderma, Raynaud's disease, arterial obliterative disease and lymphedema due to venous obstruction. There is no significant difference among them.

The highest readings for a foot in the present series were present in a patient, J. W., in whom the diagnosis of erythromelalgia was made. Comparison of his high count with the low one of his other foot is impressive (figure 4). However, when these readings are compared with those shown by a patient with scleroderma during a remission of her symptoms, the moderate difference again discourages generalization based on a single curve.

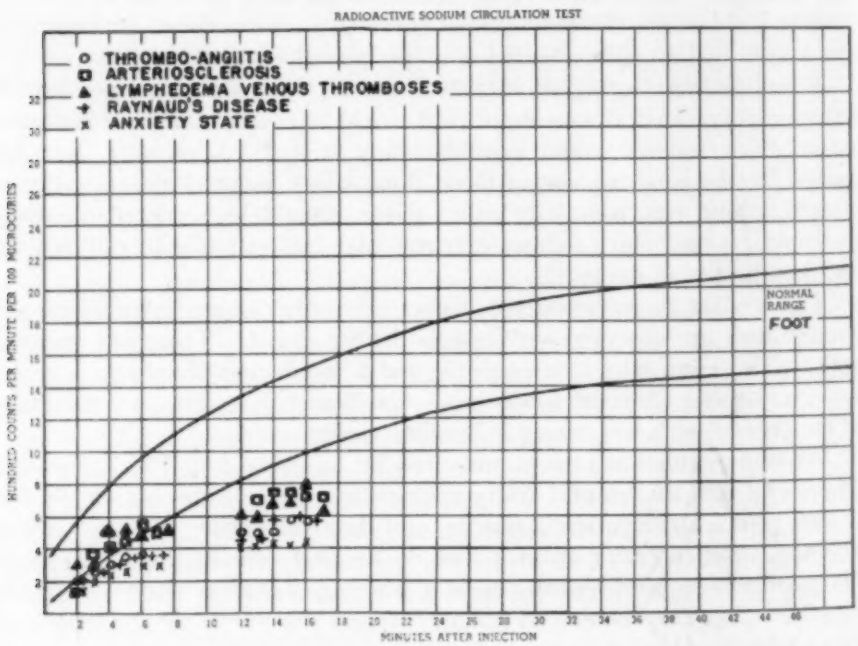

Fig. 1. The lowest curves found in a number of diverse diseases. Though these are indications of reduced blood flow, they are of no aid in differential diagnosis.

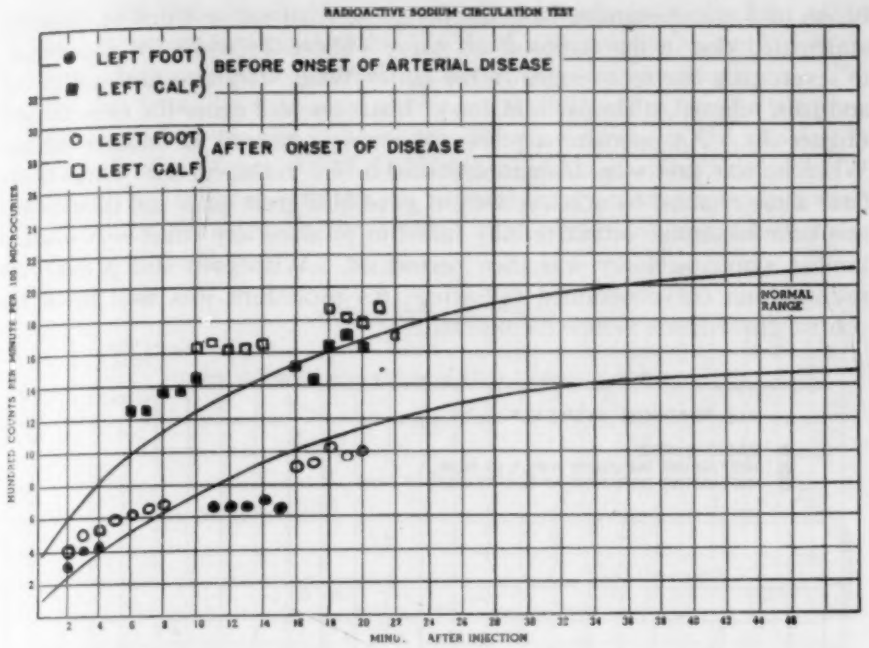

FIG. 2. Comparison of Geiger counts in left foot and calf before and after onset of arteriosclerotic obliterative disease of left popliteal artery. There is a slight fall in the count in the foot and a greater fall in the calf.

2. Contrasting Curves Made in a Single Individual during Spontaneously Changing Intravascular or Extravascular Conditions. Fortunately, it has been possible in one case to record the radiosodium count in the foot and calf of a patient before and after the development of extensive obliterative disease of his popliteal artery. Patient C. C. entered the clinic with marked reduction in walking tolerance due to an arterial block in his right leg. The left leg was asymptomatic, with good dorsalis pedis and posterior tibial pulsations and normal oscillometric readings of 2.0 in the lower half and 4.0 in the upper half of his leg. Six months later he found that his walking tolerance had suddenly become limited to one and one-half blocks by pain in the calf of his previously healthy leg. His oscillometric readings now were reduced to 0.5 in the lower half and 1.0 in the upper half of his leg. His radiosodium curve was lower than that recorded on his first visit, when he was asymptomatic (figure 2). The decrease, slight in the foot and greater in the calf, though definite, is not quantitatively as great as the reduction in his walking tolerance.

3. Contrasting Radiosodium Curves Made under the Influence of Vasodilating Agent but with a Change in Neurogenic Stimuli. Pain neutralized the effect of histamine and operative sympathectomy in two patients with severe endarteritis obliterans of the popliteal artery. An intraarterial in-

fusion of 1 mg. histamine base in 500 c.c. normal saline failed to cause the anticipated rise in the radiosodium curve (figure 3) while the patient was in severe pain due to an ingrown toe nail. When its pressure was removed and pain relieved, a similar infusion of histamine did cause the expected rise (figure 3). An opposite sequence of events occurred in another patient. When he was first seen, histamine caused a rise in the curve. Three weeks later a toe crushed by a heavy weight gave him great pain and distress and this time histamine intraarterially failed to produce any effect. A bilateral lumbar sympathectomy was then performed. With pain still present, the radiosodium curve obtained following this procedure was well below the control curve made before the operation.

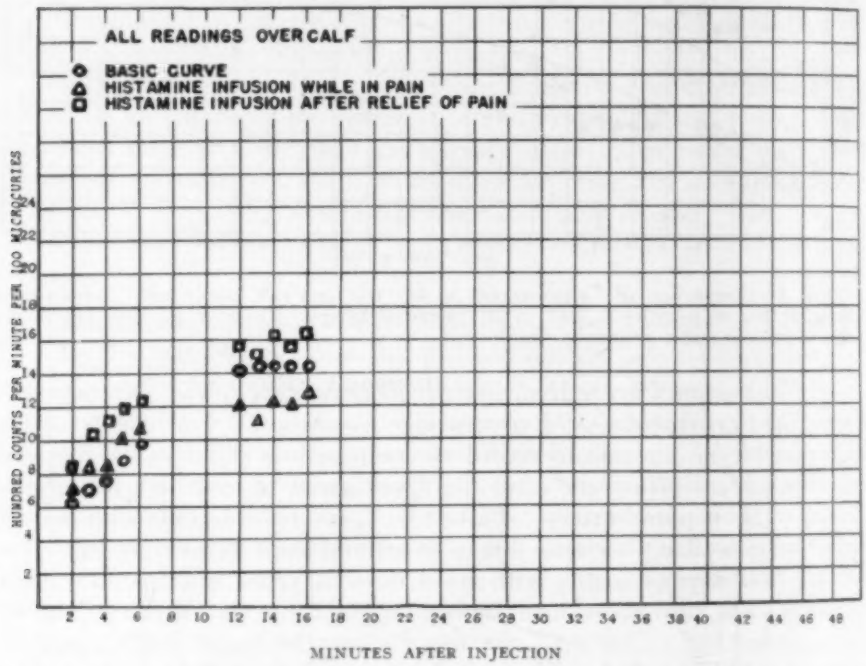

FIG. 3. Contrast in effect of intraarterial histamine infusion on Geiger count in presence or absence of pain. Only in the absence of pain is the amount significantly increased.

4. Contrast between the Basic Radiosodium Curves and Those Made under Various Experimental Conditions.

A. Arterial infusion of drugs given drop-wise.

1. *Adrenalin.* Patient M. was referred from the Orthopedic Hospital for study. A diagnosis of erythromelalgia was made because of increased skin temperatures, high oscillometric readings and burning discomfort increased by dependency and warming. There was a difference of 10° C. in skin temperature in the two feet. The exact cause of the disturbance, how-

ever, could not be determined because of lack of coöperation on the part of the patient. Roentgen-ray examination disclosed a destructive lesion in lumbar vertebrae which may have been related to the loss of vasoconstriction. The hot dry skin was like that seen after a successful lumbar sympathectomy. The difference between the radiosodium diffusion curves of the two feet is strikingly shown in figure 4. A 1:250,000 solution of epinephrine chloride given slowly by infusion into the left femoral artery caused a marked drop in radiosodium diffusion on the affected side (figure 5) and lowered the temperature of the skin 6° C.

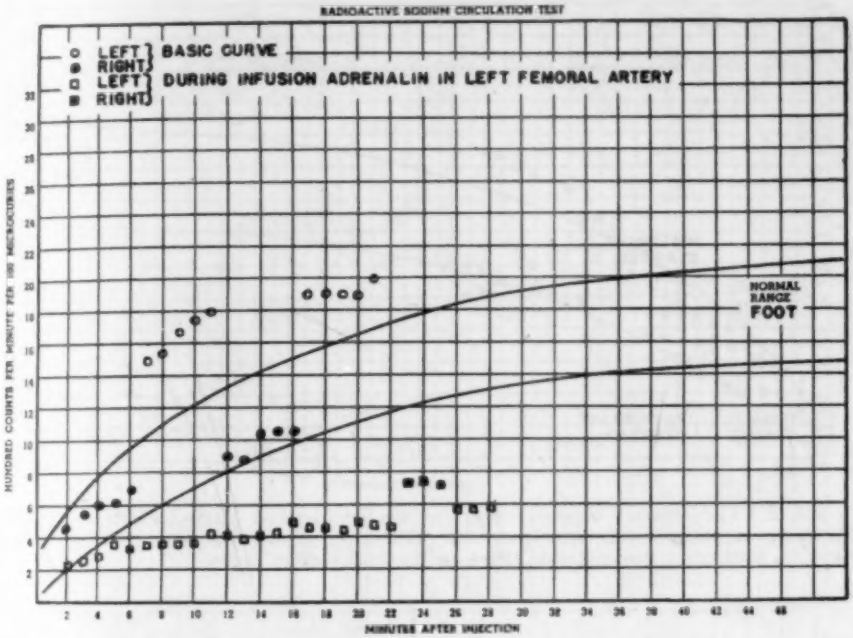

FIG. 4. Patient with erythromelalgia of left leg having much higher count on affected side. Second test made during intraarterial injection of 1:250,000 adrenalin shows marked drop on both sides.

2. *Papaverine.* The effect of papaverine on the radiosodium curve was studied in a patient whose curve could be raised by histamine (figure 5). Patient I. W. had obliterative endarteritis of the popliteal artery, with oscillometric readings of 0.2 in the lower half and 0.8 in the upper half of her leg. The test was started with the arterial infusion apparatus containing normal saline. In about eight minutes the general shape of the curve was established. At this time one of the drugs was substituted for the saline and the count continued. (This technic tests the efficacy of the drug and determines the latent period.) Histamine (1 mg. base in 500 c.c.) caused a sharp rise within six minutes. A week later, papaverine (60 mg. in 350 c.c.) showed no effect.

3. *Tetraethylammonium chloride.* The drug tetraethylammonium chloride, or Etamon, because of its ability to block chemically the sympathetic ganglia has been represented as having potential value in the treatment of peripheral vascular diseases. It has a profound effect on blood pressure and,

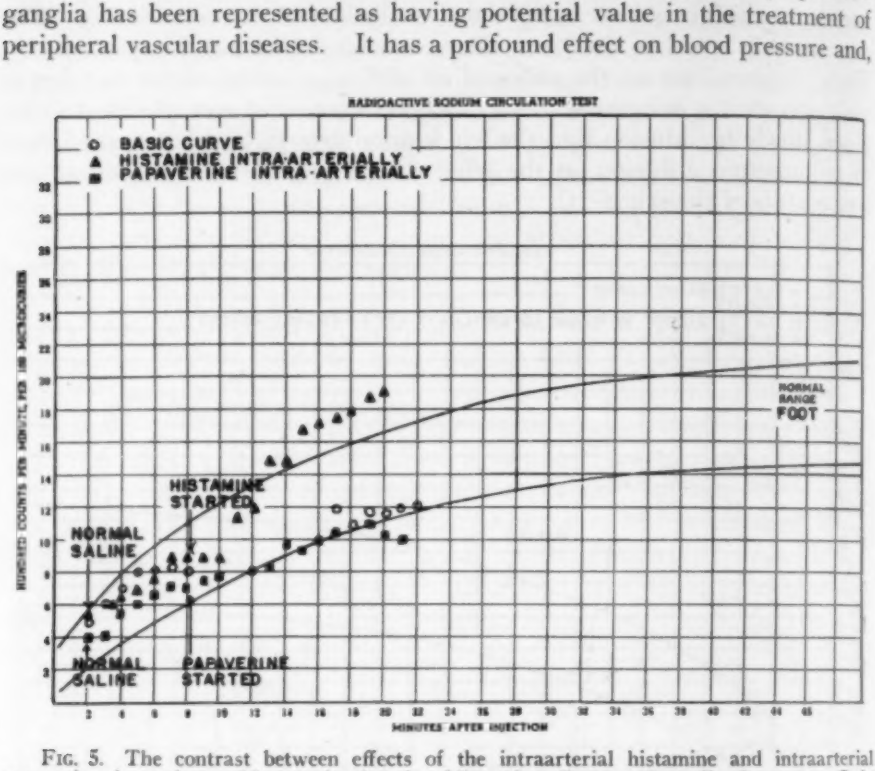

FIG. 5. The contrast between effects of the intraarterial histamine and intraarterial papaverine in patient with arteriosclerotic obliterative disease of popliteal artery. Only histamine produces a demonstrable effect on the radiosodium curve.

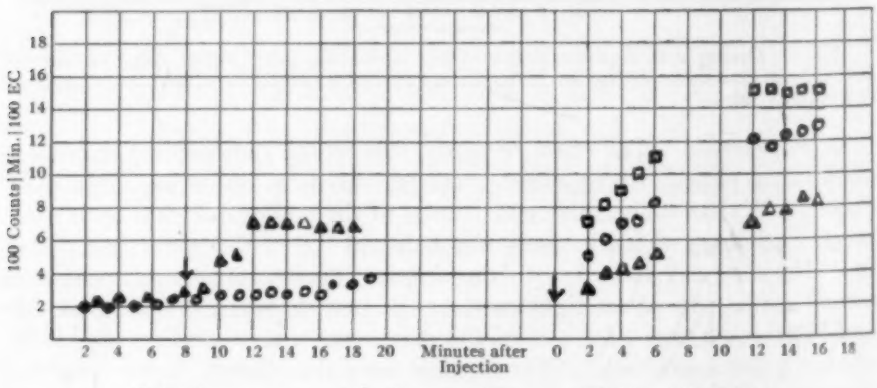

FIG. 6. Effect of "Etamon" on Geiger count. A. In normal patient 200 mg. caused a rise. B. In patient with obliterative endarteritis of popliteal artery, 500 mg. caused a drop and, by contrast, an intraarterial infusion of histamine caused a rise in same patient.

in the susceptible case, can cause a shocklike state. It was given to several patients and its effect on the Geiger count over the calf and foot was studied. Only in a normal patient who had an anxiety state did it cause a rise. In three patients with obliterative arterial disease it caused no increase or a marked drop in the count (figure 6). In one patient with Raynaud's disease it caused only an equivocal effect on his Geiger count. The arterial and venous circulation time was invariably lengthened in three cases of endarteritis obliterans of a severe degree after its use.

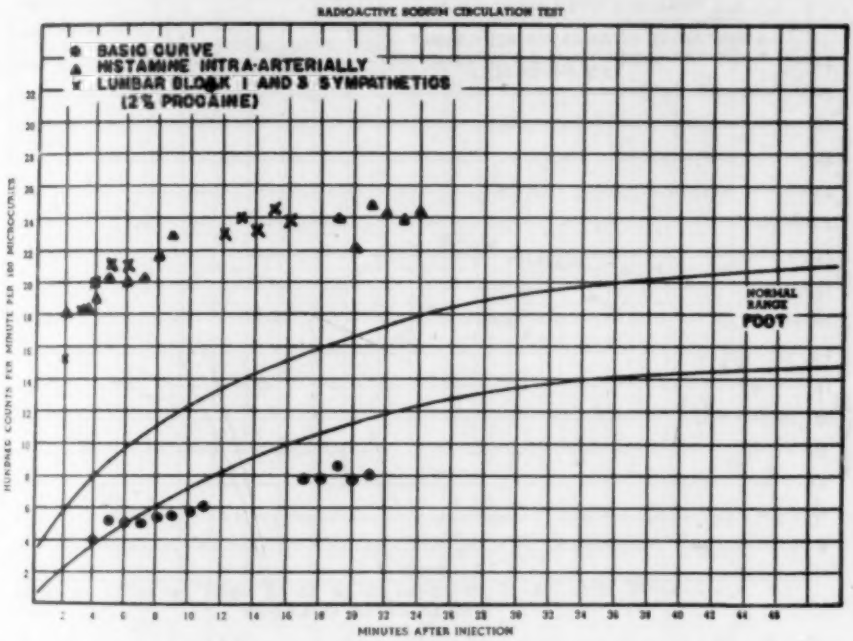

FIG. 7. The similarity of effects of intraarterial histamine and lumbar sympathetic block in patient with Raynaud's disease.

4. *Aminophylline.* This drug is a vasodilator and, unlike histamine, it is also a bronchiole dilator. After an intraarterial infusion of aminophylline, 0.2 gm. in 500 c.c. or as a single dose in 10 c.c., the drug failed to alter the Geiger count over the calves of three patients with obliterative endarteritis of the popliteal artery.

5. *Histamine.* Histamine was given by femoral artery to 24 cases of obliterative endarteritis of the popliteal artery; an increase in the Geiger count at the foot followed in 60 per cent and at the calf in 90 per cent. The relationship of this response to the clinical state and to the prognosis of repeated infusions of histamine has been studied. An increase in the count is believed to be indicative of the availability of a responsive collateral arterial

system capable of compensating for the obliterative disturbance.[7] Arterial circulation time was reduced by histamine intraarterially.

B. Sympathetic block.

Blocking the sympathetic ganglia in the lumbar region with procaine can cause a rise in the Geiger count over the foot or calf (figures 7, 8 and 9). The response is variable and dependent upon success in reaching the autonomic chain, the availability of a collateral circulation, and extravascular conditions such as pain or fear.

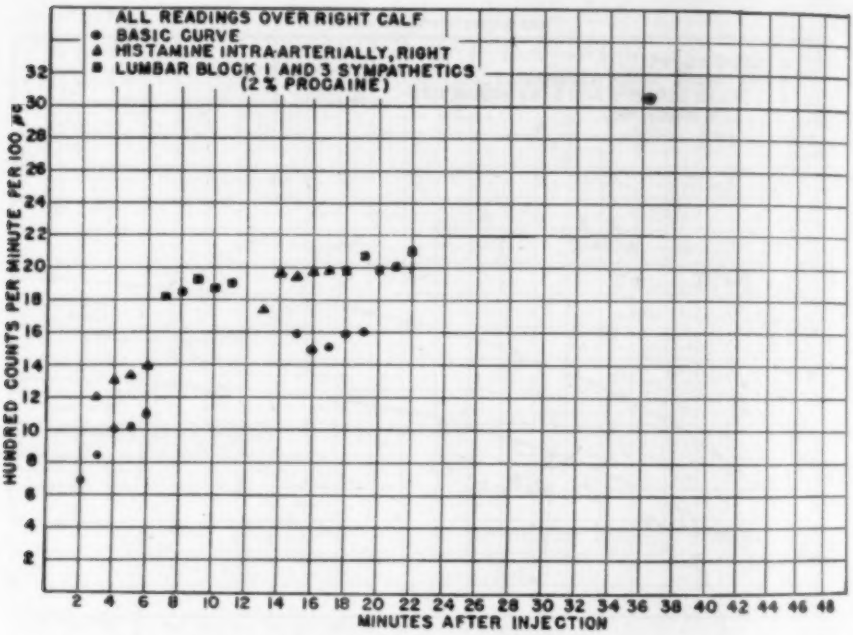

FIG. 8. The similarity of effects of intraarterial histamine and lumbar sympathetic block on measurements made over calf of patient with arteriosclerotic obliterative disease of the popliteal artery.

5. Contrast between the Control Curve and Curves Made after Histamine Intraarterially and Lumbar Sympathetic Block in the Same Patient in a Variety of Vascular Disturbances.

a. *Raynaud's disease* was present in patient M. B. In her case (figure 7), the Geiger count rose equally after both procedures. They were both accompanied by a rise in the temperature of the skin and filling of the superficial veins. However, only after histamine was there a bright erythema present from thighs to toes.

b. *Arteriosclerotic endarteritis* of the popliteal artery was the cause of disability in patient C. C. He had oscillometric readings of 0.2 in the lower half and 0.3 in the upper half of his right leg. Again the Geiger count

(figure 8) rose after both histamine and sympathetic block, although the histamine effect was more marked. Skin temperatures rose moderately in both cases and the superficial veins filled. However, only after histamine was there an erythema from the thigh to the ankle. Other individuals also with endarteritis obliterans due to arteriosclerosis or thromboangiitis were studied similarly. Their responses were variable, some showing a greater change in the radiosodium curve after block and others after histamine, but all showing erythema after histamine and none after block.

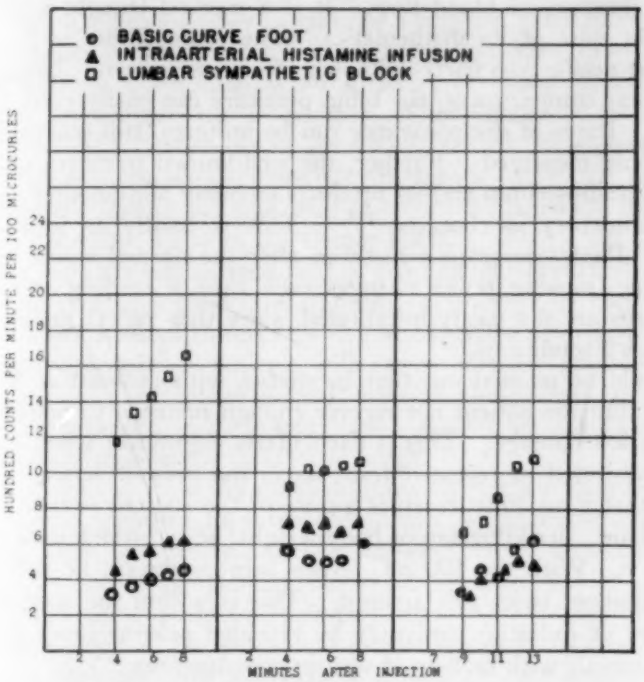

FIG. 9. The effects of intraarterial histamine and of lumbar sympathetic block on three patients with severe edema due to venous obstruction. Only the blocks caused consistent rise in the count.

c. *Chronic edema due to venous obstruction* was present in a group of patients who underwent a similar study. The response of their radiosodium curves to these procedures is seen in figure 9. In none of these cases did the histamine show an appreciable effect either in raising the sodium curve or in producing an erythema. The block, on the other hand, resulted in a marked change in the curve, but without erythema. This difference in response was unexpected because the large arteries were patent and their oscillometric readings normal.

Discussion

This use of radiosodium offers a tool for the study of peripheral circulation. Since sodium is a normal constituent of the blood, no new extrinsic influence is introduced. The radiosodium curve is a semi-quantitative measure of the flow of blood radioactively labeled. Its correlation with the A-V equilibration graphs described under "Methods" supports this. Diffusion into the extravascular compartment is not a real problem, since little sodium is introduced into the circulation and the period of observation is brief. Recently the disappearance rate rather than the appearance rate has been used as a measure of blood flow. It is a method fraught with much uncertainty in spite of its mathematics. The radiosodium is introduced by hypodermic needle into parts unknown of organs known. Intended for the extravascular compartment, the blind puncture can easily enter an arteriole or venule. Rates of disappearance can be uniform, still one cannot be sure what is being measured. Further, the well-known irritative quality of the solution of radiosodium and its products of decay add another variable, this time inflammatory in character.[3, 5, 6] This is hardly an ideal setting for accuracy. Plethysmographic methods alter the normal status by occluding venous flow, causing reflex changes each time a reading is made. Skin temperatures are not easily interpreted, since they reflect metabolic as well as circulatory conditions.

It should be pointed out that in studies with radioactive isotopes it is important that the patient not receive enough material to produce any possible radiation damage. This is particularly significant when an individual is to be subjected to repeated tests, as in the present series. It has been shown [10] that if an adult receives a dose of the sodium isotope used in this work, of 1 mC. per kilogram of body weight, he receives a total radiation of about .07 r. With the 100 mC. doses here employed, he will not receive more than about twice this amount. This is within the accepted "permissible" dose of radiation and may be repeated several times at weekly or greater intervals with no fear of serious consequences.

As demonstrated in the results, the radiosodium curve alone is not diagnostic. Individuals with different diseases may show similar curves and those with the same disease may show dissimilar curves. However, the radiosodium curves, when correlated with the patient's symptoms and signs, are often informative. Comparison of curves made on the same patient under varying conditions is most valuable. Pain may lower the curve and, even more significantly, can prevent vasodilators from being effective. This is most important, because its recognition will prevent expecting the impossible from the use of histamine or sympathectomy.[6] How fear and pain can still cause vasospasm when the sympathetics are blocked can be answered only in a speculative vein. One can predicate collateral sympathetic fibers in the spinal cord and the somatic nerve pathways which by-pass the severed

sympathetic ganglia. Only complete section of the peripheral nerve can block all the afferent and efferent impulses.

As described under "Methods," the effects of drugs on the disturbed peripheral circulation were studied by introducing a drug before or during the development of a radioactive sodium Geiger counter graph. By this method a dilute solution of adrenalin given intraarterially reduced the blood flow of the leg of a patient with erythromelalgia. Papaverine, given intra-arterially in the dose used, was ineffective where histamine, given in a similar manner, was effective. Etamon had the ability to increase the Geiger count in a normal patient. In several cases of obliterative end-arteritis it was unsuccessful where histamine succeeded. Etamon lengthened peripheral circulation time while histamine intraarterially shortened it. This response to Etamon again illustrates the fallacy of expecting a generalized vasodilatation to increase the blood flow of an extremity with partially obliterated arteries. Histamine, as previously shown,[7] when infused arterially in a dilute solution almost invariably raises the curve over the calf and less often over the foot in patients with obliterative diseases. Blocking the sympathetics can cause a rise in the Geiger count.

It has not been known in what part of the vascular system the effects of histamine and sympathectomy are initiated. However, a clue to this is offered by the unexpected differences in the experimental responses which followed these procedures in patients with severe edema caused by a chronic venous obstruction but with normal arterial circulation. Since direct microscopic observation on the experimental animal or human is not possible, we can only analyze the indirect findings.

Histamine, able to raise the radiosodium Geiger count, the temperature of the skin, and to produce an intense erythema in the vasospastic and organic arterial case, completely failed to act similarly in five patients with lymphedema. Lumbar sympathetic block did all these except produce an erythema in the same patients, including three with lymphedema. The pathologic physiology of the peripheral circulation in lymphedema is characterized by a high pressure and slowed circulation rate in the peripheral veins. When observed at the cuticle margin of the nail bed through a capillary microscope, the capillary loops are found dilated (especially their venous limbs), blood flow is sluggish, and their pressure is increased. The loops are widely separated from each other by the interstitial fluid which accumulates because of the abnormal relationship between the capillary and the blood's osmotic pressures and which is contained only by the increasing tissue pressures. Functionally this is reflected by the clinical state. The skin is cool, atrophic, prone to dissolution and ulceration after minimal trauma, easily infected and very difficult to heal. Minute vessels lying in a matrix between increased capillary and tissue pressures cannot be expected to respond normally to nutritional or chemical stimuli. Five patients who received histamine in a dose known to be pharmacologically active failed to

respond. They did not develop an erythema, a rise in the Geiger count or skin temperature. It seems reasonable to assume from the nature of their clinical and physical state that the minute vessels would not be susceptible to any stimulus. Conversely, we know histamine would have influenced these minute vessels if they had been functionally as well as anatomically available. Further, because sympathectomy did cause a rise in the Geiger count in the same patients, its action must be other than on the capillary. If the difference were only one of intensity or effect, then the block of the sympathetics in the other states, and not the histamine, should have caused an erythema. Since the reverse was true in every patient in whom their effects were contrasted, the effect of histamine must be presumed to be more formidable. Therefore, the effect of sympathetic block appears to be more central than the capillary, while the effect of histamine is on the precapillary sphincter and the minute vessels. From these observations in which radiosodium was utilized, the presence of dual pathways for peripheral blood flow appears likely: the arteriovenous anastomosis which dilates after either sympathetic block or histamine intraarterially, and the minute capillary system which sluices off arterial blood as needed for nutrition and is alone susceptible to the vasodilating effect of histamine. The existence of such dual pathways for circulating blood has anatomic proof.[9] They are functionally differentiated, the arteriovenous channels for vasomotion and the capillaries for nutrition. Clark and Clark[2] describe the development of arteriovenous anastomosis under experimental conditions, stating that they possess several layers of muscle. Their blood flow completely by-passes the capillaries. Another type of arteriovenous channel, called by Zweifach[1] "metaarterial anastomoses," are closer and more intimately associated with the capillaries. They are covered by a single layer of muscle which contracts irregularly at a rate slower than that of the heart. The capillaries are mere buds off these metaarterioles. Their blood flow is regulated by a muscle fold or sphincter at their mouths, and their distensibility is limited by the tensile strength of an endothelial coat. By this arrangement, blood flow through the metaarterial-venous anastomoses need not include passage through the capillaries. As stated above, the implications suggested by our physiologic observations and their correlation with the anatomic findings of others are put forth only as a theory. Final proof awaits direct observation.

Conclusions

1. Measurements of radiosodium diffusion are useful in the study of diseases of the peripheral vascular system and the effects thereon of various drugs of purported value. This method has confirmed the effectiveness of histamine and of sympathetic block as vasodilators in obliterative diseases of the legs. In the same patient, intraarterial papaverine, aminophylline and intravenous Etamon, in doses described in the text, were found to be ineffective where histamine intraarterially was effective.

2. The vasodilating ability of histamine and of sympathetic block can be reversed or prevented by the presence of pain.

3. The difference in the effects which have been produced by histamine intraarterially and by lumbar ganglionic block with procaine on an extremity, edematous because of a deep venous thrombus and lymphedema, has suggested the possibility that the effect of histamine is mainly on the minute vessels and capillaries, while that of sympathetic block is on the arteriovenous anastomoses.

The author wishes to express his indebtedness to the Radiological Research Laboratory, without whose coöperation the radiosodium studies could not have been carried out, in particular to Dr. Edith Quimbey for her suggestions, and to Miss Charlotte Schmidt and Mrs. Estelle Padawer for making the measurements. The author also appreciates the coöperation of Dr. Thomas Bridges for performing the lumbar sympathetic blocks. Professors Robert F. Loeb and Alfred Gilman were helpful with their critical review of this paper.

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CALCIFIC AORTIC STENOSIS SIMULATING ACUTE CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION *

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A considerable literature dealing with calcific aortic valvular disease has accumulated since Mönckeberg's classic paper of 1904. For a complete bibliography and a review of the significant articles the reader is referred to recent monographs by Karsner and Koletsky [1] and by Kumpe and Bean.[2]

The present report concerns itself with one of the manifestations of this disease which, although mentioned casually by a few writers,[3, 4] has not received the emphasis it merits. We refer to the occasional development of severe, prolonged chest pain with shock and collapse, producing a picture clinically identical with that of acute coronary thrombosis and myocardial infarction.

This communication is prompted by the observation within a short period of time of three cases with calcific aortic stenosis exhibiting the above symptom complex. In all of these the diagnosis of coronary thrombosis with myocardial infarction was made clinically, even though in two of the cases the existence of the aortic lesion was known.

Case Reports

Case 1. A 55 year old widow, while at work as a bookkeeper, was seized suddenly with severe, crushing, substernal pain radiating to the neck and left arm. Several hypodermic injections of morphine were required to relieve the agonizing pain.

Her son, a physician, stated that to his knowledge his mother had not been previously under medical care, although on moderate exertion she had appeared somewhat breathless and at times had complained of slight precordial discomfort.

Upon examination six hours after the onset of the attack she was still in severe pain. She exhibited ashen pallor, the face and body were covered with perspiration, and her pulse at the wrist could not be palpated. At the cardiac apex the heart sounds were faint, the rate was rapid and the rhythm was totally irregular. No murmurs could be heard. Despite oxygen and morphine, shock was profound and death occurred 12 hours after the onset of the attack.

The electrocardiogram (figure 1) showed auricular fibrillation, average ventricular rate 160, and changes characteristic of preponderant left ventricular hypertrophy.

Despite the absence of electrocardiographic changes indicative of acute myocardial infarction, such a diagnosis was made ante mortem because the clinical picture

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was so typical of this condition. However, the anatomic diagnosis established at autopsy was (1) rheumatic heart disease with calcific aortic stenosis and mitral stenosis with minimal insufficiency; (2) myocardial hypertrophy and dilatation, and (3) pulmonary hyperemia and edema. There was some atherosclerosis of the coronary arteries, but no occlusion or significant arterial narrowing was found and no myocardial infarction was present.

Case 2. A 57 year old white male laborer entered Multnomah County Hospital because of dyspnea and ankle edema.

During the preceding five years the patient had had numerous episodes of cardiac decompensation which responded to ordinary measures. He had had frequent attacks of crushing precordial pain which were relieved by nitroglycerin.

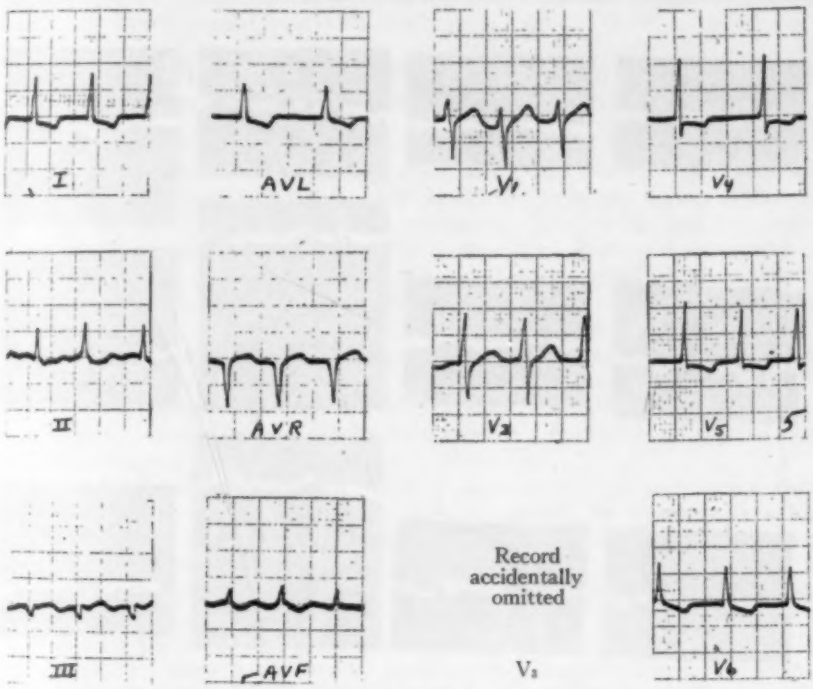

FIG. 1. *Case 1,* age 55, August 5, 1947. Calcific aortic stenosis.

On admission to the hospital the temperature was 98.4° F., respiration 24, pulse 84, and blood pressure 142 mm. Hg systolic and 94 mm. diastolic. The chest was emphysematous in type and there were moist râles in both lung bases. The heart was moderately enlarged to the left. There was a high-pitched, crescendo systolic murmur heard over the entire precordium. This murmur was loudest in the mitral area and was transmitted to the axilla. There was also a softer, decrescendo systolic murmur at the aortic area which was transmitted into the neck vessels. The liver was palpable 3 cm. below the costal margin; its edge was smooth. There was ankle edema.

Routine measures for the treatment of cardiac decompensation were instituted.

Five days after admission the patient complained of persistent pain in the upper left chest. On physical examination he appeared to be in shock. He was dyspneic and the skin was moist and cool. A diagnosis of acute coronary occlusion with myocardial infarction was made. Anticoagulants were started.

An electrocardiogram (figure 2) taken during the attack of pain showed evidence of preponderant left ventricular hypertrophy but no changes diagnostic of acute myocardial infarction. The tracing was identical in pattern with one taken two days prior to the onset of the present attack of pain.

The patient was treated as a case of acute myocardial infarction and was kept on anticoagulants for three weeks. On this regimen he appeared to improve; but on the twenty-first day after the onset of the acute attack he suddenly developed a paroxysm of dyspnea, became very cyanotic and, despite positive pressure oxygen and other emergency measures, died two hours later.

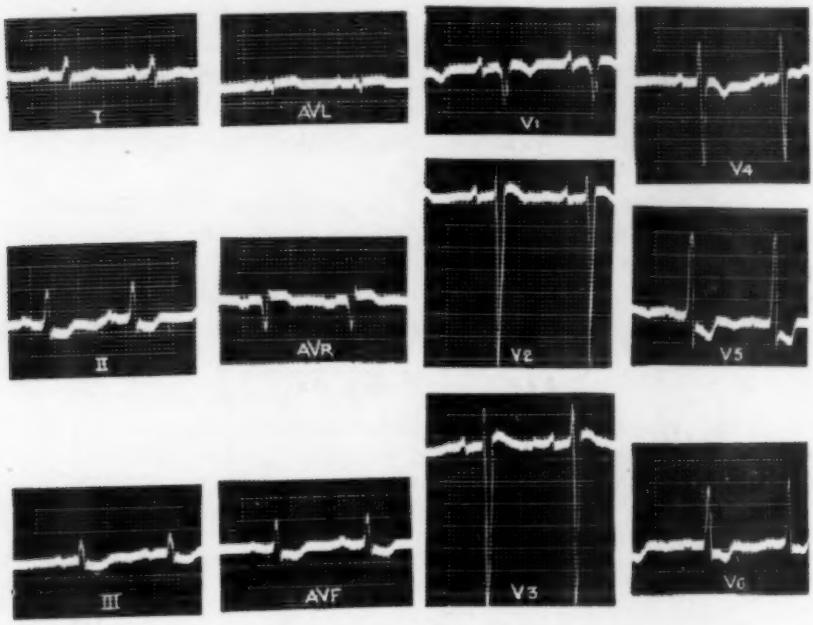

FIG. 2. *Case 2,* age 57, January 23, 1948. Calcific aortic stenosis.

The anatomic diagnosis established at necropsy was calcific aortic stenosis, hypertrophy and dilatation of all chambers of the heart, and pulmonary edema. There was moderate arteriosclerosis of the coronary arteries, but no occlusion of a major branch and no infarction of the myocardium were present.

Case 3. A 71 year old white male laborer entered Multnomah County Hospital because of dyspnea, orthopnea and ankle edema. His symptoms had started four years previously and had been controlled by digitalis until a few months before admission.

Physical examination on admission disclosed signs of severe congestive failure, including fluid in the pleural and peritoneal cavities. The blood pressure was 125 mm. Hg systolic and 35 mm. diastolic, pulse 90, temperature 98° F., respiration 20, and the heart was enlarged 12 cm. to the left of the midsternal line. A harsh, loud sys-

tolic murmur was heard over the apical and aortic areas with transmission into the vessels of the neck. The aortic second sound was absent.

Paracentesis of the thorax and abdomen was performed shortly after admission, and routine measures for treatment of cardiac decompensation were instituted.

The progress in the hospital was satisfactory until the ninth hospital day, when the patient suddenly experienced severe pain in the left chest which lasted about one hour. The pain was accompanied by dyspnea, profuse diaphoresis and a picture of shock. Oxygen and intravenous morphine were given. A diagnosis of acute coronary occlusion and myocardial infarction was made. An electrocardiogram was not taken. He died 24 hours later.

The anatomic diagnosis established at necropsy was calcific aortic stenosis, dilatation and hypertrophy of the heart, and old, healed rheumatic mitral valvulitis. There were generalized arteriosclerosis and coronary arteriosclerosis, but no coronary occlusion and no myocardial infarction.

In addition to the above case reports, the following record is of interest even though autopsy confirmation is not available.

Case 4. A vigorous male, aged 57 years at death, had been under observation for a period of 20 years. From the beginning there were clinical signs of an aortic lesion, and in later years typical "dancing" calcifications in the region of the aortic valve were repeatedly demonstrated fluoroscopically. During the last five years of life, on several occasions the patient suffered attacks of prolonged substernal pain, radiating to the neck and arms and requiring morphine for relief. The attacks were associated with signs of shock and collapse and in all respects resembled acute coronary thrombosis. However, within 24 to 48 hours after the subsidence of the pain, recovery was complete with no demonstrable changes in the blood count, sedimentation rate or the electrocardiogram. The latter on repeated examination exhibited a constant pattern of left bundle branch block, but at no time during or after the severe attacks was there any significant variation from the usual pattern or any other change suggestive of acute myocardial infarction.

The attacks usually occurred at night without significant provocative factors. Between attacks, from which he always recovered rapidly, he was capable of great exertion without discomfort; against advice, he often played more than 18 holes of golf on each of two or three successive days.

The final attack occurred during an emotional episode, with death following shortly after the onset of pain. Autopsy was not permitted.

The earliest electrocardiogram available was taken 12 years before death. That tracing exhibited a pattern which may be interpreted as preponderant hypertrophy of the left ventricle or incomplete left bundle branch block. In the course of the ensuing two years, the pattern changed gradually to complete left bundle branch block and remained essentially unaltered in configuration until death.

At the time of the first electrocardiogram, the heart was "borderline" in size or only very slightly enlarged. During the succeeding 12 years the heart increased in size continuously, and before death became enormously enlarged.

The evidence in this case for calcific aortic stenosis was beyond question. Unfortunately, in the absence of anatomic confirmation, associated severe occlusive coronary disease cannot be completely excluded. Yet clinically the resemblance to the three proved cases is striking.

We have observed two more cases which may well fit into this category. They are not included in this report, however, because of complications (a

phlegmonous gastritis in one and a ruptured aortic valve cusp in another) which cast doubt on the origin of the pain, even though the pain was sufficiently typical of acute myocardial infarction to cause such a diagnosis to be made ante mortem.

Discussion

The question of to what extent associated coronary arterial disease may have been responsible for the severe and fatal attacks of cases 1, 2, or 3 demands consideration. This question cannot be answered dogmatically. However, in our experience with clinicopathologic material extending over a span of more than 30 years, such severe and fatal attacks were not encountered in cases with similar degree of coronary atherosclerosis in the absence of valvular disease or other gross cardiac lesion.

Furthermore, autopsy records of other cases with calcific aortic stenosis whose histories contained no mention of pain were examined for comparison. The same and even higher degrees of coronary atherosclerosis were recorded for the cases without pain. The lack of correlation in these cases between the degree of coronary disease and the incidence of pain corresponds to observations of other authors.[1, 2]

The occurrence of precordial or anginal pain in aortic valvular disease has long been recognized.[1, 2, 3, 4] From various records it has been estimated that such pain occurred in "from 10 to 42 per cent of the cases."[1] However, that pain and shock of the type and extent described in this report may be encountered in these cases is less generally appreciated. The incidence of this symptom complex is not possible to estimate at this time. It is hoped that this report will stimulate further study and observation which may provide the answer to this question.

The problem of diagnosis merits some comment. It is obvious from the protocols herein recorded that the general clinical features may be identical with those occurring in acute coronary occlusion with myocardial infarction. However, some help in diagnosis may be derived from (1) a history or signs of aortic valvular disease, and (2) an electrocardiographic pattern of preponderant left ventricular hypertrophy which fails to develop changes characteristic of myocardial infarction. Either one alone of the above features may not be sufficient to establish the diagnosis of this specific symptom complex. However, the occurrence of the two together seems to us strong evidence against myocardial infarction and favors the assumption that the aortic lesion is the major cause of the attack. From our own experience and from an examination of the cases recorded in the literature,[3, 4, 5] we feel that electrocardiographic changes suggestive of acute myocardial infarction do not occur in calcific aortic stenosis in the absence of myocardial infarction; the development of such electrocardiographic changes favors the diagnosis of myocardial infarction regardless of the presence or absence of signs of an aortic lesion.

It is true that Master, Jaffe and Dack [3] report one case of aortic stenosis with precordial pain in which the electrocardiogram was "characteristic of coronary thrombosis." This was in 1937. In the light of more recent knowledge, the tracing in question would be interpreted more properly as denoting preponderant left ventricular hypertrophy and probably also digitalis effect. It suggests myocardial ischemia, but not acute myocardial infarction.

Summary

Cases with calcific aortic disease are reported in which there occurred prolonged, severe anginal type of pain with shock and collapse, presenting a picture clinically identical with that of acute coronary occlusion and myocardial infarction. Various clinical, pathologic and electrocardiographic features are discussed.

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TYPHUS AT BELSEN. II. CLINICAL COURSE OF EPIDEMIC TYPHUS IN PERSONS WHO HAD RECEIVED CRAIGIE TYPHUS VACCINE*

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BRITISH troops who took part in the recent war in Europe were inoculated with Craigie typhus vaccine. During the typhus epidemic at Belsen in 1945, at least 14 of them contracted the disease. This provided an opportunity to observe naturally acquired epidemic typhus in persons who had received Craigie typhus vaccine. The primary purpose of this paper is to describe the clinical course of their illness with data on their previous inoculations and serologic responses.

In the same epidemic, there were 16 cases of typhus among Hungarian soldiers who were inoculated with Craigie vaccine after exposure to the disease. There were also 41 cases of typhus in German soldiers and nurses who had had no immunization against typhus. Data were obtained on them which make it possible to estimate the value of Craigie vaccine under epidemic conditions.

THE NATURE OF CRAIGIE TYPHUS VACCINE

The early attempts to produce immunity to typhus have been reviewed by Zinsser.[1] In general, they were cumbersome and expensive. Cox's[2] demonstration that rickettsiae could be grown in the chick embryo opened the way to large scale preparation of typhus vaccine. The original method of Cox and Bell,[3] modified to utilize the ether extraction process of Craigie[4] and to include the soluble antigen of Topping and Shear,[5] served as the basis on which millions of doses of typhus vaccine were produced for the American armed forces. This vaccine, commonly called Cox vaccine, contains the soluble antigen and killed bodies of the rickettsiae of epidemic typhus (*R. prowazeki*). Its effect on louse-borne typhus has been reviewed by Ecke et al.[6] and Sadusk.[7]

Typhus vaccine for the British and Canadian Armies was prepared at the Connaught Laboratories in Toronto under the supervision of Dr. James Craigie. This product, which will be referred to as Craigie vaccine, was

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It is a pleasure to acknowledge the unfailing coöperation of Lt. Col. M. W. Gonin, D. S. O., R. A. M. C., who collaborated in these studies. I am also indebted to Major C. J. Zarafonetis, M. C., A. U. S., who was responsible for the serologic examinations, to Dr. Ruth Pitt-Rivers, who made the determinations of NPN, and to many at Belsen who helped in the care of typhus patients under epidemic conditions.

prepared by methods similar to Cox vaccine, but it differed in some of the details as well as in antigenic structure. In its manufacture, after the yolk sacs of infected chick embryos had been homogenized and diluted with saline, the mixture was set at pH 7.0. To this, 50 per cent ether was added and the whole frozen by CO_2 ice and then thawed to break up the protein-lipoid complex. The rest of the process was similar to that outlined by Topping [8] for commercial laboratories in the United States. For potency tests, Craigie vaccine was given to mice which were later challenged by the intravenous injection of live rickettsiae.

Craigie, Watson, Clark and Malcomson [9] had found "that mice may be actively immunized against the toxic factors of murine and epidemic rickettsiae. The immunity produced by small doses of vaccine is type specific." Both types of rickettsiae were grown at the Connaught Laboratories, and their antigens prepared, tested, and mixed in the ratio of two parts epidemic material to one part murine material in the final product.

Craigie vaccine was, therefore, a polyvalent vaccine containing the soluble antigens and killed bodies of both epidemic typhus rickettsiae (*R. prowazeki*) and murine typhus rickettsiae (*R. mooseri*). So far as known, no description of the clinical course of typhus in Craigie vaccinated persons nor evaluation of this vaccine under epidemic conditions has been published.

Exposure of British Workers to Typhus

The typhus epidemic at the concentration camp in Belsen, Germany, has been described in a previous paper [10] which dealt with its control. It is sufficient to repeat that there were about 3,500 cases of typhus among the 45,000 living inhabitants of the larger camp when it was liberated in April, 1945. Practically all of these survivors were heavily infested with lice.

Among the first to enter this camp were 68 British medical workers who distributed food, carried out the sick, and deloused the inmates. All of the 68 were heavily exposed to typhus patients, their lice, and the louse feces on their clothes. Twelve of them contracted typhus during the course of the work. Other British and Allied workers were exposed to a lesser degree. Among them, one soldier who shaved the heads of the sick and one volunteer nurse contracted the disease.

Because none of the British had previously been exposed to typhus, all possible precautions were taken. The immunization records of all who entered Belsen were checked and it was ascertained that all had received prophylactic immunization. All who entered the concentration camp were regularly powdered with DDT powder and instructed in precautions against lice. Men were given adequate time for rest and the maintenance of their personal hygiene. Thus it can be stated that the British cases here reported, with one exception, were seasoned soldiers in excellent health and nutrition who contracted typhus under the heavy exposure of an epidemic after having had a series of three or more injections of Craigie typhus vaccine. The

single exception (case 15) was a Red Cross volunteer nurse; her case will be reported in detail.

Methods of Study and Care

The German military hospital at Belsen had been taken over for the sick who were evacuated from the concentration camp, but one wing was reserved for members of the Allied forces. As soon as any soldier reported sick with a fever he was hospitalized there. Patients with fever or headache, except those with surgical conditions or common diarrheas, were considered typhus suspects. All suspects were seen daily by Lt. Col. Gonin or the author, usually by both together. A daily record of their illness was kept on prepared forms. Signs and symptoms were graded from 1 to 4 plus. "Fever" was considered to be an oral temperature over 98.6° F. (37° C.).

The basis of the studies was detailed clinical observation. A routine blood count was made on most patients, usually on the second hospital day. Roentgenograms of the chest were taken in a few cases. Acute and convalescent sera were taken on all typhus suspects and sent to Major Zarafonetis for examination at the Cairo Laboratory of the United States of America Typhus Commission. Dr. Pitt-Rivers made blood examinations for non-protein nitrogen on 10 patients.

Treatment was simple, being based on general nursing care. Patients were given bed rest, large amounts of fluids, as much food as they would take, and three multi-vitamin capsules daily. Aspirin, codeine or morphine were administered in moderation for headache or cough, as well as occasional sedatives.

Diagnoses were based on the final results of clinical and serologic findings. The severity of the illness was classified as nearly as possible in accordance with the criteria used by Ecke et al.[6] but using descriptive terms as follows:

Very mild: "Cases so mild a definite diagnosis of typhus on clinical evidence alone was not possible."

Mild: "Cases with minimal symptoms and signs, yet definitely diagnosed as typhus on clinical evidence."

Moderate: "Cases of moderate severity, showing slight prostration, central nervous system involvement, cardiovascular changes, or mild complications." This was taken to mean cases with no more than a 2 plus prostration or 1 plus typhus state as judged at Belsen.

Severe: "Severe typhus cases, with marked prostration, central nervous system involvement, cardiovascular changes, or serious complications." This was taken to include cases with 3 plus prostration or 2 plus typhus state as judged at Belsen.

Very severe: "Cases so severely ill that a fatal outcome was expected at some point in the clinical course."

Fatal: "Fatal cases."

Clinical Observations on British Cases

The positive findings on 14 cases of typhus fever in British personnel who had all received inoculations of Craigie vaccine before exposure to the disease are summarized in tables 1 and 2. For each degree of clinical severity an example is given.

Case Reports

Case 2. Typhus, severe. Patient was a 35 year old sergeant in the 11th Light Field Ambulance, British 2nd Army. Past history was not contributory. He denied previous exposure to typhus. He had had three injections of Craigie typhus vaccine (1 ml. each) given on January 8, 1944, January 30, 1944, and February 4, 1945. From April 22 on he had been in charge of the stretcher bearers removing the sickest cases from Belsen. As such he went into the huts and examined, lifted and undressed patients who were taken out to the hospital. He had been powdered twice daily with 5 per cent DDT and had never found lice on his body.

On May 11 (first day of disease) he had a rapid onset of cough, headache, prostration and fever. Temperature was 102.2° F., pulse 100; he was hospitalized.

On the second day he complained of severe headache and prostration. Physical examination revealed a man of good nutrition and excellent physique. The only signs found were a dry cough and scattered râles in the chest, but he seemed acutely ill. Blood count was reported as hemoglobin 84 per cent; red blood cells 3.8 million, white blood cells 7,000, with 74 per cent polymorphonuclears, 21 per cent lymphocytes, 4 per cent monocytes, and 1 per cent eosinophils. The red cells appeared normal. He was put on bed rest, forced fluids and a light diet, supplemented by three multivitamin capsules per day.

On the third day he was worse. His fever reached 104.8° F., with pulse 100. Severe headache, cough and râles were as before. His skin appeared dry, and about 20 pale pink petechiae which blanched on pressure were noted on his chest, abdomen and the inner surface of the arms. He was urged to drink fluids and was given aspirin for the headache. Serologic specimen taken this day showed no agglutinins against Proteus OX-19; the serum for complement fixation tests was lost.

On the fourth day he had the same high fever and prostration. Typhus state was noted, so he was helped to drink. The rash was more apparent but had not increased in area or size of petechiae.

On the fifth day his temperature reached 104.8° F. for the third consecutive day. His skin was drier, his prostration deeper, his spleen palpable two fingers below the costal margin, his liver tender, and he had rigors. Headache diminished somewhat and cough was not noted, perhaps due to weakness. Morphia (gr. .25) was given for sleep.

On the sixth day he presented the picture of severe typhus with marked prostration, typhus state and delirium. He vomited once. Headache diminished, perhaps because he was too sick to complain. Cough and râles had disappeared.

On the seventh day his condition was about the same.

Blood count showed 5,400 white blood cells, with 62 per cent polymorphonuclears, 36 per cent lymphocytes and 2 per cent monocytes. Blood culture was negative. Non-protein nitrogen was 39 mg. per cent.

On the eighth day little change was noted. His temperature was lower on this day and he denied headache, though he was delirious at night. The rash became darker and he had three bowel movements. He was still assisted in feeding and drinking but required no medication.

On the ninth and tenth days he appeared his weakest. There were definite

TABLE I

Typhus in 14 British Given Craigie Vaccine before Exposure

Case Number	Age and Sex	Exposure as	Date of Onset and Days from Exposure	Vaccine			Serologic Tests				Estimated Severity	Presenting Complaints
				Total Given in ml.	Dates of First and Last Doses	Days from Last Dose to Fever	Day of Disease	Epidemic	Murine	Weil Felix (OX-19)		
1	35 m	bearer	May 8 17 days	4	Jan. 8, 44 Feb. 3, 45	94	4 14	1/40 1/320	1/20 1/160	1/20 1/1280	Mild	Fever, pain in back of neck
2	35 m	bearer	May 11 21 days	3	Jan. 8, 44 Feb. 4, 45	96	11 16	1/160 1/320	1/160 1/160	1/320 1/1280	Severe	Cough, headache, prostration, fever
3	34 m	bearer	May 9 18 days	3	Jan. 8, 44 Feb. 3, 45	95	3 13	1/40 1/640	1/10 1/80	0 1/1280	Moderate	Fever, weakness, headache
5	38 m	shaving	May 12 19 days	4	Jan. 16, 43 Mar. 15, 45	58	10 15	1/640 1/2560	1/320 1/320	1/640 1/320	Moderate	Frontal headache, stiffness in legs
6	29 m	bearer	May 6 15 days	4	Jan. 8, 44 Feb. 4, 45	91	7 14	1/20 1/640	1/10 1/160	0 1/80	Moderate	"Ordinary cold," fever, headache, profuse sweating
7	28 m	bearer	May 5 14 days	4	Jan. 14, 44 Feb. 2, 45	92	18	last 1/1280	1/320	1/640	Mild	Frontal headache, pain in lumbar region
9	30 m	bearer	May 7 16 days	4	Feb. 28, 44 Feb. 3, 45	93	5 15	1/40 1/1280	1/40 1/640	1/80 1/1280	Moderate	Headache, vomiting, slight cough

TABLE I—*Continued*

Case Number	Age and Sex	Exposure as	Date of Onset and Days from Exposure	Vaccine			Serologic Tests				Estimated Severity	Presenting Complaints
				Total Given in ml.	Dates of First and Last Doses	Days from Last Dose to Fever	Day of Disease	Epidemic	Murine	Weil Felix (OX-19)		
10	30 m	feeding sick	May 6 15 days	3	Sept. 7, 43 Jan. 31, 45	95	7 17	1/40 1/640	1/20 1/160	1/80 1/320	Mild	Weakness, fever, severe headache
11	30 m	physician	May 8 17 days	4	Feb. 7, 44 Mar. 3, 45	66	5 15	1/40 1/160	1/20 1/80	1/40 1/160	Mild	Headache, nasal discharge, fever, prostration
13	20 m	bearer	May 9 18 days	4	Nov. 8, 44 Feb. 5, 45	93	3 18	0 1/640	0 1/320	0 1/80	Moderate	Headache, fever, weakness
14	27 m	powderer	May 9 18 days	5	Jan. 1, 44 Apr. 12, 45	27	3 13	1/80 1/1280	1/80 1/640	1/160 1/160	Mild	Headache, cough, fever
15	56 f	nurse	May 14 21 days	2	Feb. 17, 45 Feb. 24, 45	79	6 13	1/320 Q.N.S.	1/80 Q.N.S.	1/40 1/160	Mild	Cough, fever, chest pain, burning on micturition
16	25 m	powderer	May 14 19 days	4	Jan. 5, 44 Apr. 20, 45	24	4 8	1/40 1/160	1/20 1/80	0 0	Mild	Headache, malaise, fever
18	28 m	bearer	May 15 21 days	3	Jan. 6, 44 Feb. 4, 45	100	5 16	1/80 1/2560	1/40 1/640	1/40 1/1280	Very mild	Headache, nausea, fever, pain in neck
Mean	31.8		17.8 days	3.6		78.8	5.6 14.6	1/50 1/675	1/29 1/220	1/22 1/258		

TABLE II

Typhus in 14 British Given Craigie Vaccine before Exposure

Case Number	Estimated Clinical Severity	Days of Fever	Day Allowed Up	Maximum Observed Fever °F.	Maximum Observed Pulse Rate	Admission Blood Count		Headache		Rash		Dry Skin		Dry Tongue		Cough		Râles in Chest		Enlarged Spleen		Prostration		Typhus State	
						Total WBC	% Polys.	First Day Noted	Days Duration	First Day Noted	Days Duration	First Day Noted	Days Duration	First Day Noted	Days Duration	First Day Noted	Days Duration	First Day Noted	Days Duration	First Day Noted	Days Duration	First Day Noted	Days Duration	First Day Noted	Days Duration
1	Mild	6	12	102.0	94	8,000	60	4	4	5	4	4	3	3	3	4	3	none	0	none	0	3	4	none	0
2	Severe	11	16	104.8	110	7,000	74	1	7	3	11	3	9	none	0	1	12	2	9	5	6	1	15	4	8
3	Moderate	8	15	103.4	92	8,600	55	1	9	3	6	4	6	5	5	5	4	7	2	7	2	5	5	7	3
5	Moderate	7	12	103.0	100	—	—	1	5	2	2	3	2	6	1	3	3	3	2	5	2	3	6	5	2
6	Moderate	10	15	104.0	90	4,600	64	1	9	5	4	6	2	none	0	6	3	6	3	none	0	6	4	7	3
7	Mild	9	12	101.8	104	—	—	1	11	5	2	5	4	4	2	8	3	none	0	none	0	7	3	none	0
9	Moderate	13	17	103.8	96	7,600	75	1	10	5	5	4	12	4	10	1	7	4	5	none	0	3	7	4	3
10	Mild	8	12	103.2	102	7,300	58	1	10	8	4	5	3	4	3	4	3	4	3	none	0	5	3	none	0
11	Mild	8	9	102.6	112	—	—	1	7	4	3	4	4	4	2	3	5	3	3	none	0	5	2	none	0
13	Moderate	11	14	103.8	100	6,600	74	1	12	3	5	4	5	4	3	5	3	5	3	7	3	1	10	4	5
14	Mild	7	11	102.4	100	5,500	51	1	4	3	3	4	2	none	0	1	6	none	0	none	0	none	0	none	0
15	Mild	8	12	102.4	100	6,650	59	?1	?7	4	3	5	3	4	3	?1	?5	4	3	none	0	none	0	none	0
16	Mild	8	8	103.2	90	—	—	1	4	4	4	2	2	none	0	2	2	2	3	none	0	none	0	none	0
18	Very mild	8	11	103.4	90	6,800	70	1	6	none	0	none	0	none	0	5	2	5	2	none	0	none	0	none	0
Mean	Mild to moderate	8.7	12.6	103.1	98	6,865	64	1	7.5	4.2	4.3	4.1	4.4	4.2	3.5	3.5	4.4	4.1	3.6	6.0	3.2	3.9	5.9	5.1	4.0

(Based on cases where sign was present.)

changes in his physical signs. His pulse became slower, delirium disappeared, and the spleen diminished in size. Cough and râles reappeared.

On the eleventh day he was somewhat better. Temperature and pulse were lower, râles disappeared, the prostration and mental confusion were less, the spleen was no longer palpable, and he took more fluids. A serum specimen taken this day showed a titer of 1/320 against Proteus OX-19, and complement fixation titers of 1/160 against both epidemic and murine typhus antigens.

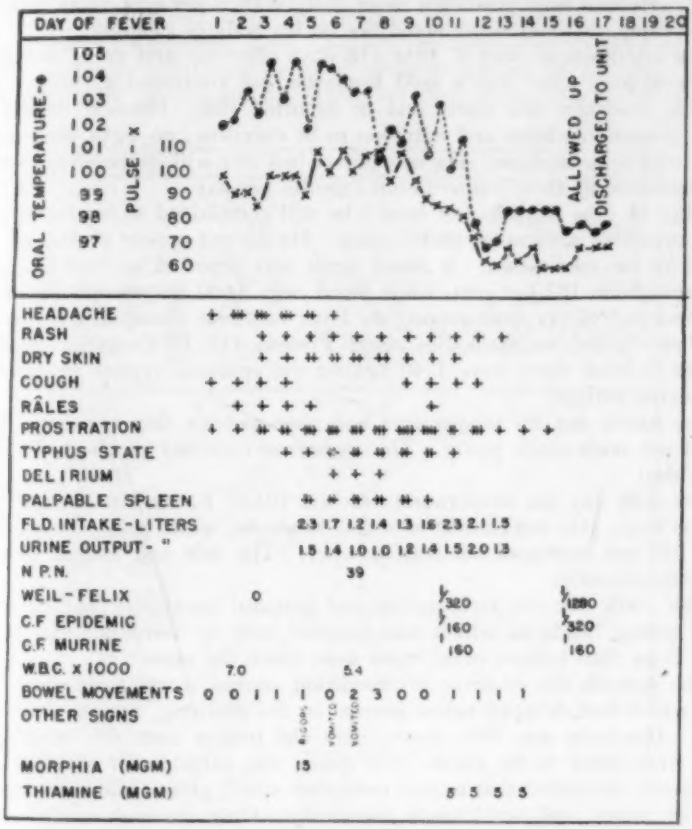

FIG. 1. *Case 2.* Typhus, severe, onset May 11, 1945.

Because of the prolonged fever, injections of thiamin chloride (5 mg. daily) were begun. In retrospect, these seem valueless. On the twelfth day a dramatic improvement was apparent. His mind had cleared and his fever had gone. The only remaining signs were a faint rash, minimal cough and prostration. He slept most of the day; this sleep was sound and deep, in contrast to the fitful rest of the previous week.

From that time on, convalescence was uneventful. On the seventeenth day he was discharged to his unit. A serum specimen taken that day showed agglutination of Proteus OX-19 in a dilution of 1/1280, complement fixation titers of 1/320 against epidemic and 1/160 against murine rickettsial antigen.

Case 3. Typhus, moderate. Patient was a 34 year old private who served in the 11th Light Field Ambulance, British 2nd Army. Past history was not remarkable; a native of England, he had never been exposed to typhus before reaching Belsen but had had three injections of Craigie typhus vaccine (1 ml. each) given on January 8, 1944, January 29, 1944, and February 3, 1945. He had first entered the concentration camp on April 21, 1945, and had worked there regularly as a stretcher bearer until the onset of fever. His job was to go into the huts, strip the patients who had been selected for hospitalization, wrap them in blankets, and carry them to an ambulance. He had been powdered twice daily with 5 per cent DDT powder as he entered the camp, and had never noted lice on his body or clothing.

On the afternoon of May 9, 1945 (18 days after his first entry into the camp) he noted weakness, fever and a mild headache, but continued at work. The next morning his headache was worse and he reported sick. Physical examination revealed his general condition and nutrition to be excellent; no signs were noted other than fever and some malaise. He was put at bed rest with forced fluids and a light diet, supplemented by three multivitamin capsules per day.

On May 11 (the third day of fever) he still complained of headache, and a few faint pink petechiae were noted on his chest. He did not appear ill, but sat up in bed and asked for no medication. A blood count was reported as: red blood cells 5.5 million, hemoglobin 102 per cent, white blood cells 8,600, polymorphonuclears 55 per cent, lymphocytes 44 per cent, monocytes 1 per cent; no abnormal cells seen. Serologic studies showed no antibodies again Proteus OX-19 (negative Weil Felix); complement fixation titers were 1/40 against the epidemic typhus antigen and 1/10 against murine antigen.

On the fourth day his temperature had risen and his skin was noted to be dry, but he did not seem much worse. The rash now consisted of about 20 easily seen pink petechiae.

On the fifth day his temperature reached 103.6° F., and he seemed prostrated for the first time. He complained of severe headache, which was relieved by aspirin. The rash had not increased but was browner. The skin and tongue were dry; he coughed intermittently.

On the sixth day his temperature had dropped somewhat, but he complained of a very severe headache which was relieved only by morphia. His tongue was somewhat drier than before; other signs were about the same.

On the seventh day of fever his condition seemed worse than ever. The temperature, which had dropped below normal in the morning, rose to 101° F. in the afternoon. Headache was very severe, skin and tongue were dry, cough continued and râles were noted in the chest. His spleen was palpable for the first time. To his prostration was added that mental confusion which gives typhus its name, though he could be roused and could speak coherently. Only the rash seemed milder; no new petechiae were noted, and the old brownish spots were less easily seen.

On the eighth day he seemed about the same, although the temperature had come almost to normal and his headache had abated. Subsequent events showed this to be the last day of fever.

On the ninth day after the onset of the disease a dramatic change was apparent. His temperature remained normal, headache had diminished, the cough, râles, enlarged spleen and rash had gone, and he seemed greatly improved. Although there were still prostration and the typhus state, these seemed to be a residual fatigue. He slept through much of the day. Blood which was examined showed non-protein nitrogen of 32 mg. per cent and a titer of 1/40 against Proteus OX-19.

On May 18, 10 days after the onset of the fever, all signs of disease had gone and an uneventful convalescence began. Blood taken 13 days after the onset of fever, and

five days after the fever had gone, showed agglutinins against Proteus OX-19 in a dilution of 1/1280 and rise in titer of the complement fixation tests as compared with the acute blood specimen. (Titer of 1/640 against the epidemic antigen and 1/80 against the murine antigen.)

He was allowed up on the fifteenth day and discharged to active duty on the nineteenth day.

Case 15. Typhus, mild; rheumatic heart disease, inactive, with mitral stenosis and insufficiency; dysentery, etiology unknown. Patient was a 56 year old English woman. Since 1927 she had had "heart disease with a murmur." In 1940 she had been made deaf by an exploding bomb. Despite these disabilities, she had persistently sought and finally gained acceptance as a volunteer worker in a British Red Cross ambulance unit. For several months before reaching Belsen she had noted dyspnea

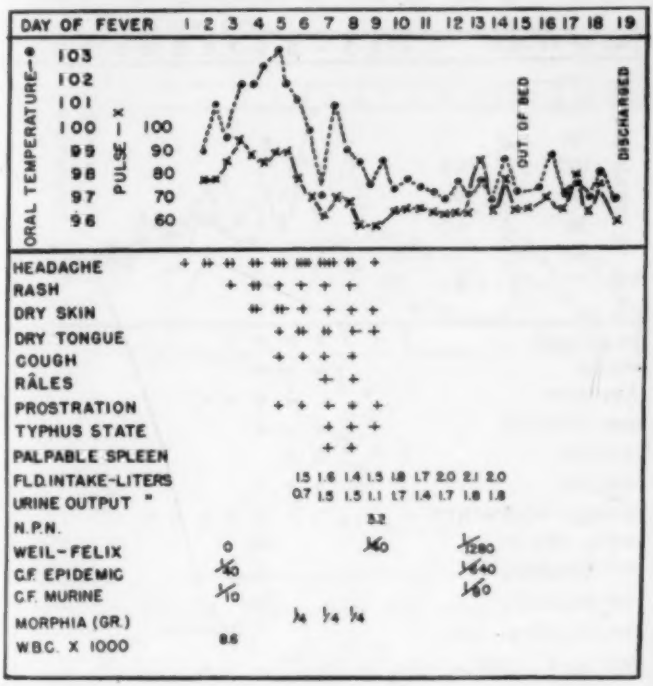

FIG. 2. *Case 3.* Typhus, moderate, onset May 9, 1945.

on exertion and swelling of her ankles after exercise but had not mentioned these signs. For three weeks before her illness she had nursed "clean" typhus cases who had been deloused and washed.

She had never been exposed to typhus before reaching Belsen, claimed that she had never entered the concentration camp, and had been powdered with DDT daily. How she contracted the disease is not ascertainable, but a few lice were found in the hair of some patients in her area of the hospital. She had received two injections of Craigie typhus vaccine, of 1 ml. each, on February 17 and 24, 1945.

On May 14, 1945, she noted fever, cough, pain in the chest, and a burning pain on micturition. Not until May 17 (fourth day of disease) did she report sick, spending the first three days of her illness mostly at rest but getting up for meals.

Physical examination showed an elderly woman who insisted she was well except for a little cough and mild headache; temperature 102.4° F., pulse 88. There was a sparse petechial rash on the abdomen and her tongue was dry. Hearing was markedly diminished bilaterally. The chest had coarse moist râles throughout both bases. The cardiac apex was in the mid-clavicular line, and there were diastolic and systolic murmurs heard best at the apex. Diagnosis of typhus was made and cardiac decompensation suspected. She was put on bed rest with a light diet.

On the fifth day of illness her temperature had fallen, and she claimed to be quite well except for the cough and increasing headache due to it. Signs included a scant petechial rash, dry skin and tongue, cough and râles. Blood count was reported as: red blood cells 4.56 million; white blood cells 6,650, 59 per cent polymorphonuclears, 35 per cent lymphocytes, 4 per cent monocytes, 1 per cent eosinophils, 1 per cent basophils. No abnormal cells were seen.

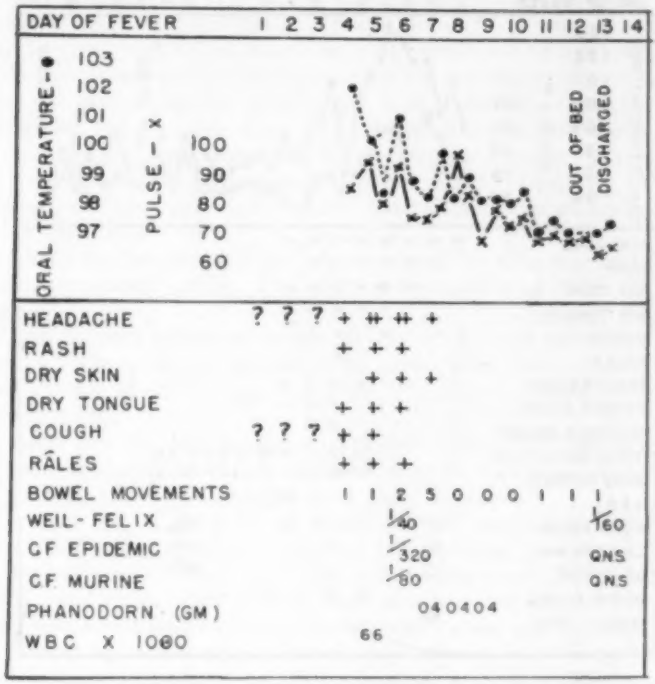

FIG. 3. *Case 15.* Typhus, mild, onset May 14, 1945.

On May 19 she still had marked headache but her rash was fading and she no longer coughed. Serum showed agglutination against Proteus OX-19 in a dilution of 1/40, complement fixation titers of 1/320 against epidemic typhus and 1/80 against the murine typhus antigen.

On the seventh day her rash, dry tongue and râles had gone. On this day she had a mild diarrhea, consisting of five loose bowel movements. Nevertheless she claimed to feel well, except for a minimal headache, and asked for sleeping tablets.

On the eighth day (May 21) all signs of disease had gone. On the thirteenth day of her illness, after six days of convalescence in bed, she was allowed up and discharged to her unit. No signs of malaise were noted, though the cardiac murmurs

were still present. A blood specimen showed a titer of 1/160 against Proteus OX-19; unfortunately, the quantity which arrived in Cairo was not sufficient for other tests.

Case 18. Typhus, very mild. Patient was a 28 year old private in the 11th Light Field Ambulance British 2nd Army. Past history was not remarkable. A native of England, he had never been exposed to typhus but had had three injections of Craigie typhus vaccine (1 ml. each) on January 6, 1944, January 13, 1944, and February 4, 1945. He first entered the concentration camp on April 21 and worked irregularly as a stretcher bearer there. He had been powdered at the time of each entry into the camp and never found lice on himself.

On May 11, 1945, he noted some mild headache, a sensation of nausea, pain in the neck and feverishness. These symptoms were mild and he did not report sick. On May 12, 13 and 14 he continued at light work in the "human laundry," though he felt indisposed and sat down between chores. On the evening of the fourth day of illness (May 14) his temperature was 102° F. He spent that night in his tent, entering the hospital the next day.

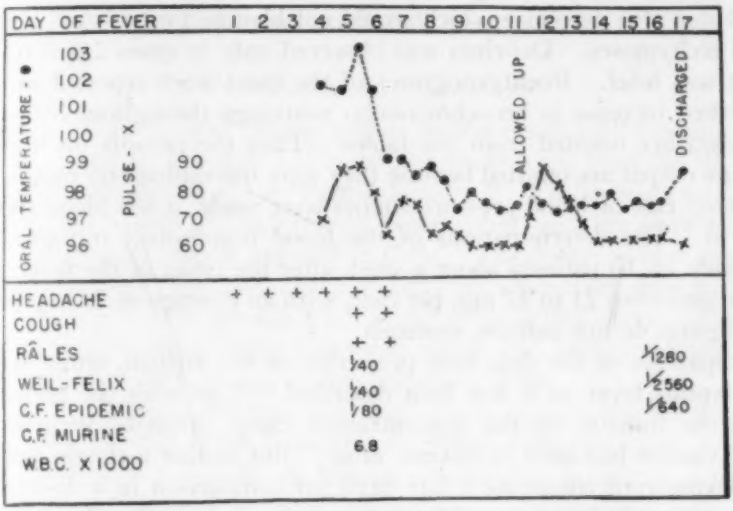

FIG. 4. *Case 18.* Typhus, very mild, onset May 11, 1945.

On the fifth day he complained only of mild headache and malaise. Physical examination revealed him to be in excellent condition, not acutely ill, and only a slight nonproductive cough and a few scattered râles in the chest were noted. Temperature 101.8° F., pulse 88, respirations 18, hemoglobin 100 per cent; red blood cells 4.7 million, white blood cells 6,800, with 70 per cent polymorphonuclears, 26 per cent lymphocytes, 4 per cent monocytes. He was given bed rest, light diet and forced fluids. On the sixth day he seemed the same; no rash had appeared, and his fever fell to 99.2° F. in the evening. By the seventh day he seemed completely well. On the tenth day he was allowed up, and was discharged on the seventeenth day.

No diagnosis on clinical grounds was possible, though a mild respiratory disease seemed most likely. Blood specimens taken on the fifth and sixteenth days showed marked increases in titer against the specific antigens. Agglutinations with Proteus OX-19 rose from 1/40 to 1/1280; complement fixation with epidemic typhus rose from 1/40 to 1/2560, and with the murine antigen from 1/80 to 1/640.

It can be seen that the cases fit more or less into a pattern similar to classical epidemic typhus but distinctly milder and briefer, with no deaths and no serious complications. Detailed inspection reveals considerable variation between individuals. There was one case (case 2) so severe that it resembled the classical disease, and one (case 18) so mild that it might have been called "just a touch of grippe." Clinical signs did not always appear or disappear in the same order, nor were they exactly correlated in time or severity. Case 3 comes close to serving as the average case, if such could be described.

The absence of most of the serious complications of typhus from the tables is significant. Parotitis, gangrene, conjunctivitis, deafness due to typhus, epistaxis, pulmonary consolidation and pleuritic pains were never observed in the British, although all were to be seen in the typhus patients from the concentration camp. Their rash was never extensive, rarely developed into true petechiae which would not blanche on pressure, and never formed ecchymoses. Delirium was observed only in cases 2 and 6, and in these it was brief. Roentgenograms of the chest were reported as normal or "marked increase in bronchovascular markings throughout both lungs." Some data are omitted from the tables. Thus the records on fluid input and urine output are omitted because they were incomplete; no routine urine, respiratory rate or blood pressure studies were made; a few blood specimens were lost. The determinations of the blood non-protein nitrogen, which were made on 10 patients about a week after the onset of the fever in each case, ranged from 21 to 42 mg. per cent, with an average of 29 mg. per cent. These figures do not indicate azotemia.

Comparison of the data here presented on the British, either with epidemic typhus fever as it has been described [11, 12] or with the typhus cases among the inmates of the concentration camp, strongly suggested that Craigie vaccine had been of distinct value. But neither a classic description nor starving men constitute a fair basis for comparison in a disease which is known to vary from one epidemic to another. It is therefore convenient to present data on the Hungarian and German soldiers before further discussion.

Typhus in Hungarian Soldiers

About 432 Hungarian soldiers were used as laborers at Belsen. These men had never been exposed to typhus, nor had they been immunized against it. Beginning on April 23, groups of them entered the concentration camp to assist the British soldiers. They took the same preventive measures as the Allied troops, including powdering with DDT, but could not be given vaccine until April 29. On that date or the next, all Hungarian soldiers were given 1 ml. of Craigie vaccine intramuscularly. Most of them were given a second injection on May 4.

There were 16 known cases of typhus among the Hungarians. Ten of these were from a group of 57 who had worked side by side with the British

as powderers and had had the heaviest exposure. Two had been stretcher bearers and four had been sanitary laborers. Medical care was given them in a German military hospital 20 miles from Belsen. All were examined at least once by the author and their cases reviewed with their physician. It was clear that all had had a rash, fever and prostration, but none had died or had serious complications. An estimate of the severity of each case was made and a convalescent blood specimen taken. There were nine mild cases, four moderate cases, and three severe cases; none was very mild, very severe, or fatal. The results are shown in table 3.

It is emphasized that the Hungarians do not constitute a control group for comparison with the British as regards the value of the vaccine. Rather, they are another group of similar age, sex, nutrition, exposure and care, who are particularly characterized by the fact that they received their first vaccine 16 days or less before contracting the disease. Most were in the incubation period when they were inoculated.

Typhus in the Germans

There were 41 cases of clinical typhus in non-immunized German nurses and work troops at Belsen. Thirty-two of these were from the 48 nurses who had washed the sick in the "human laundry." The patients were naked when brought to them by the stretcher bearers, but head lice were abundant and the nurses were heavily exposed to them. These nurses were powdered regularly with DDT, but the powder was quickly washed off their hands and arms. They were not immunized, having refused treatment. The other nine German cases were soldiers, none of whom had been immunized, who had been sanitary laborers in the concentration camp.

When the Germans fell sick they were given care in the same hospital by the same physicians as the Hungarians. They were seen twice, their case reviewed, and estimated as to the clinical severity in conjunction with their German doctor. Among the nurses there were no atypical mild fevers likely to have been "very mild" typhus, 14 "mild" cases, 11 "moderate" cases, one "severe" case, five "very severe" cases, and one fatal case in a woman 43 years of age. Their average age was 25 years, and the average duration of fever was 14.5 days for the survivors. Among the soldiers there were three "moderate" cases, five "very severe" cases, and one fatal case in a man 52 years of age. Their average age was 29 years, and the average days of fever of the survivors were 16.3. The severe and very severe cases had weak and rapid pulse; prolonged delirium and partial deafness were seen.

The data on the Germans provide the only available evidence as to the severity of typhus at Belsen in persons who were neither protected by vaccine nor debilitated by starvation. The question arose: Was typhus at Belsen as severe as that seen in other epidemics? Probably the best basis for comparison between epidemics is provided by the death rate as corrected

TABLE III

Typhus in 16 Hungarian Soldiers Given Craigie Vaccine after Exposure

Case Number	Age and Sex	Exposure as	Date of Onset	Days from Exposure	Vaccine			Clinical Data		Serologic Tests			
					Total Given in ml.	Dates Given	Days from Vaccine to Fever	Days of Fever (Over 37.0° C.)	Estimated Clinical Severity	Day of Disease	Epidemic Antigen	Murine Antigen	Weil-Felix (OX-19)
1	35m	bearer	May 3	11	1	April 29	4	14	Mild	20	1/10	Neg.	1/640
2	22m	laborer	May 15	?	1	April 29	16	14	Mild	8	1/40	1/20	1/2560
3	32m	powderer	May 3	11	1	April 29	4	15	Mild	20	1/80	Neg.	1/10240
4	22m	powderer	May 8	16	1	April 29	9	14	Moderate	16	1/80	Neg.	1/640
5	35m	bearer	May 3	12	1	April 29	4	14	Severe	20	1/320	1/10	1/1280
6	38m	powderer	May 8	16	2	April 29 May 4	9, 4	14	Severe	16	1/320	1/10	1/160
7	30m	laborer	May 13	?	1	April 29	14	9	Mild	10	1/160	Neg.	1/10240
8	22m	powderer	May 8	15	1	April 29	9	13	Mild	16	1/320	1/40	1/10240
9	30m	powderer	May 5	13	2	April 29 May 4	6, 1	14	Moderate	18	1/160	1/20	1/5120
10	22m	laborer	May 14	?	1	April 29	15	15	Severe	10	1/320	1/20	1/640
11	32m	powderer	May 3	10	1	April 29	4	14	Mild	20	1/640	1/40	1/5120
12	34m	powderer	May 9	17	2	April 29 May 4	10, 5	12	Mild	14	1/160	1/40	1/5120
13	31m	powderer	May 7	15	2	April 29 May 4	8, 3	14	Moderate	16	1/160	1/40	1/1280
14	36m	powderer	May 7	14	2	April 29 May 4	8, 3	14	Moderate	16	1/320	Neg.	1/320
15	18m	powderer	May 6	14	2	April 29 May 4	7, 2	14	Mild	17	1/640	1/320	1/1280
16	23m	laborer	May 8	?	1	April 29	9	14	Mild	15	1/1280	1/40	1/2560
Mean	28.8			13.7	1.4		8.5	13.6	Mild to moderate	15.8	1/182	1/11	1/1719

for age and sex. By assigning to each of the German cases an "expected fatality" equal to the average fatality as observed in other epidemics for the appropriate age and sex, such a comparison has been made. There were two observed deaths among the Germans at Belsen; their "expected deaths" according to typhus as observed by Murchison [11] (p. 237, table 15) in London from 1848–1870 were 5.95, as observed by Soper et al.[13] in Naples in 1943–1944 were 5.39, and observed by Ecke et al.[6] in Cairo were over 6.2. Another basis for comparison is provided by the average duration of fever in unvaccinated and untreated patients who survived. This was 14.9 days in the Germans at Belsen; it was 13.4 days in 500 cases observed by Murchison [11] in London, 13.8 days in 14 cases observed by van den Ende et al.[14] in Naples in 1943–44, and 18.1 days in a group of 47 Egyptians studied by Ecke et al.[6] While it is fully realized that a group of 41 persons with only two deaths is not large for comparative purposes, and that differences such as nutrition and care cannot be controlled, this evidence suggests that Belsen typhus was a relatively nonfatal form of the disease which had approximately the normal time course.

Discussion

The difficulties and pitfalls attendant on the field trial of any vaccine for human beings, partly indicated above, are too well known to be reiterated here. For this discussion it is assumed that the British, Hungarians and Germans were comparable as to exposure, nutrition, hospitalization and medical care. Data as to their age, sex, immunization, duration of fever, outcome and diagnosis could be confirmed by investigation. The available evidence for their comparison is shown in table 4.

It is immediately apparent that no deaths occurred in persons who had been vaccinated, but that there were deaths in the nonvaccinated group. This is not, however, statistically significant, due to the small size of the groups and the low death rate.

Table IV

Comparison of Typhus in Three Groups at Belsen

Number and Group	Vaccination History	Age in Years	Fever Duration in Days	Deaths
14 British	2 to 5 doses all given more than 24 days before illness	20–56 Av. 31.8	6–13 Av. 8.7 0.488	0
16 Hungarians	1 to 2 doses, none given more than 16 days before illness	18–38 Av. 28.8	9–15 Av. 13.6 0.340	0
41 Germans	no vaccine	20–52 Av. 25.9	13–24 Av. 14.9 0.343	2

The second point which can be seen is that the duration of the fever in the British was much briefer than in the Germans. These figures are highly significant, the difference between the two groups being 10.3 times the standard error of the difference. Coupled with the clinical observations, they lead to the conclusion that *two or more doses of Craigie vaccine (1 ml. each given 24 or more days before the onset of louse-borne typhus reduce the severity and shorten the course of the disease.* This conclusion is similar to that reached by the Cairo Unit of the United States of America Typhus Commission [6] concerning Cox vaccine.

The third point noted is that the duration of fever in the Hungarians was 1.3 days less than in the Germans. This difference, though small, is 2.68 times the standard error of the difference. Combined with the clinical observations, this makes it probable that as little as one or two doses of Craigie vaccine, given after exposure to typhus, were of some value in lessening the severity of the illness. This adds further weight to the growing evidence that vaccination against typhus is of value even during an epidemic. It is very strong evidence against the concept of a "negative phase," or belief that vaccine given during the incubation period is harmful.

It is probably not wise to draw further conclusions from the data presented. Since only epidemic typhus was present at Belsen, the value of the murine component in Craigie vaccine did not receive trial. The marked and early rise in the complement fixing antibodies against the murine antigen does not separate the two vaccines, since numerous authors have shown that there is some degree of cross fixation, though it suggests that Craigie vaccine may be of value against murine typhus. The time from exposure to fever in the British is longer than the incubation period of typhus, but this may have been due to several things. It is obvious that Craigie vaccine did not prevent typhus, and there is no definite evidence that it diminished the incidence. There is no clear correlation between the number of injections of vaccine or time from the last dose and either the duration or the severity of the disease. The mildest case had had his last booster dose 100 days before the onset of fever, and the woman of 56 who had only mild typhus had had only 2 ml. of Craigie vaccine.

Summary

During the typhus epidemic at Belsen, 14 cases of typhus in persons who had had Craigie typhus vaccine more than 24 days *before* the onset of their fever were studied. Their clinical courses are given in detail.

Also, 16 cases of typhus in soldiers who had received only one or two doses of Craigie vaccine *after exposure* to typhus, and 41 cases of typhus in well nourished Germans who had had no vaccine were observed.

It is concluded that Craigie vaccine was of definite value in shortening the course and reducing the severity of epidemic typhus fever when given in two or more doses from 24 to 100 days before the onset of typhus, and

possibly of value even when given during the incubation period of the disease.

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LIVER AND SPLEEN VISUALIZATION BY A SIMPLE ROENTGEN CONTRAST METHOD *

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THERE can be little question of the diagnostic value of roentgen visualization of the size, shape and position of the liver and spleen. A number of methods have been described previously for its accomplishment. The simple abdominal flat plate will frequently demonstrate partial outlines of these organs, if stomach and intestinal gas shadows are fortuitously present. Displacements of the barium-filled digestive tract may provide the clue to liver or spleen enlargements. Thus, an enlarged spleen displaces the stomach to the right and produces a smooth pressure defect on the greater curvature; the colon is displaced downward and to the right. The barium-filled stomach wall may be seen to extend into the notch of an extremely enlarged spleen. Liver enlargements may displace the stomach and duodenal bulb to the left, downward and posteriorly; may cause a pressure defect on the upper surface of the bulb and on the lesser curvature of the stomach, and may depress the hepatic flexure and proximal transverse colon downward, with compression of their superior surface. Such displacements and compressions, being due to enlargements not directly visualized, may not easily be differentiated from extra-enteric masses of other origins.

More definitive visualization of these organs has been attempted by contrast technics. Pneumoperitoneum,[1] accomplished by injection of large quantities of air, oxygen or carbon dioxide, allows determination of liver and spleen size in most cases, and is useful as well in determining the presence of adhesions, distortions and tumor masses. It is sufficiently traumatic, however, to warrant its use only in selected cases. Colloidal thorium dioxide (thorotrast),[2] injected intravenously in quantity determined by body weight, is deposited in the cells of the reticuloendothelial system and produces dense shadows of liver and spleen on the roentgenogram. This procedure is of particular diagnostic value in cirrhosis, abscess or tumors in the liver because of the differential thorotrast densities produced within the liver shadow. It is not without danger, however, because of long continuing radioactivity and the possible undesirable effects of blocking the reticuloendothelial system. Its use is best restricted to aged or carcinomatous patients, since endothelial cell sarcoma of the liver [3] and aplastic

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From the Medical and Roentgenologic Services, Winter Veterans Administration Hospital.
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anemia [4] have been reported 12 and 10 years subsequent to its injection in apparently well authenticated cases. More such reports are to be expected, in view of the deleterious effects of thorotrast observed in animals.[5] More recently, colloidal organic iodine compounds have been used by intravenous injection to achieve a similar effect, which is transient. Visualization of the liver and spleen by this means also depends on blocking of the reticuloendothelial system. The patient must be tested for iodine sensitivity. Berg [6] reports slight fever occurring in one-third of his cases, and occasionally high fever, chills, cyanosis and drop in blood pressure.

The method described here involves none of these objections. It is routinely applicable, essentially free of trauma, and presents no dangers. Gastrointestinal bleeding or perforation are considered its only contraindications. It is essentially an improvement of the ordinary abdominal flat plate roentgenogram, in which the occasionally helpful gas shadows are deliberately reinforced. We have performed over 140 * of these examinations thus far, with no ill effects other than a rare complaint of mild abdominal cramping of brief duration. Examination is best performed with the stomach empty, though this is not essential. Colonic preparation is not needed. The patient is given one-half to one Seidlitz powder mixture in separate one-third glassfuls of water, and asked to retain the stomach gas without belching until the roentgenograms have been made. Alternatively, we have used carbonated soft drinks, but these are somewhat less satisfactory. The drink is followed immediately by injection of air into the colon by rectal tube and bulb, continued until the patient is aware of a feeling of fullness; greater distention than this is not necessary. The patient also holds this air until completion of the examination.

Roentgenograms are made in the standing position, using the posteroanterior view for optimal liver visualization and the left oblique view for optimal spleen visualization. We have found the posterior and anterior left oblique views to be equally satisfactory, due to the nearly central location of the body of the spleen. An obliquity of approximately 30 degrees has been found most satisfactory. Films are exposed at 40 inch distance, in the expiratory phase of respiration, using an upright Bucky grid, with an exposure time of one-half second at 100 ma., kilovoltage varying with body thickness but being usually 65 to 75 kv. for the PA view and 5 kv. greater for the oblique view. The central ray is directed through the midepigastrium (eleventh or twelfth dorsal vertebra).

The lower border of the liver extends down normally to approximately the level of the costal arch. Pfahler,[7] in a study of 502 subjects, using flat films of the abdomen at a 25 inch distance, described these measurements of normal liver size: the "length" of the liver, measuring from its lower right edge to the highest point of the upper border, averaged 21.3 cm., with normal limits of 18 to 22 cm.; the "width" measured from the highest point

* Now approximately 500.

of the right lobe to the midpoint of the lower border, averaged 12.8 cm. with normal limits of 10 to 14 cm. (figure 1). Measurements on our films, taken at 40 inch distance, should be somewhat smaller.

In another study,[1] using pneumoperitoneum, spleen length of 10 cm. was considered as average normal. Dell and Klinefelter [8] found the width of the normal spleen as seen in the PA projection to be 5 to 5.5 cm. They considered the spleen to be enlarged if measuring 6 cm. or more, if greater than 85 per cent the size of the kidney, or if denser than the normal kidney. Their measurement of width was made at the broadest visible point of the shadow, measured to the outer border of the spleen, when this was visible, or to the internal surface of the ribs, when the border was not visible. They found considerable variation in the size of the normal spleen in different individuals.

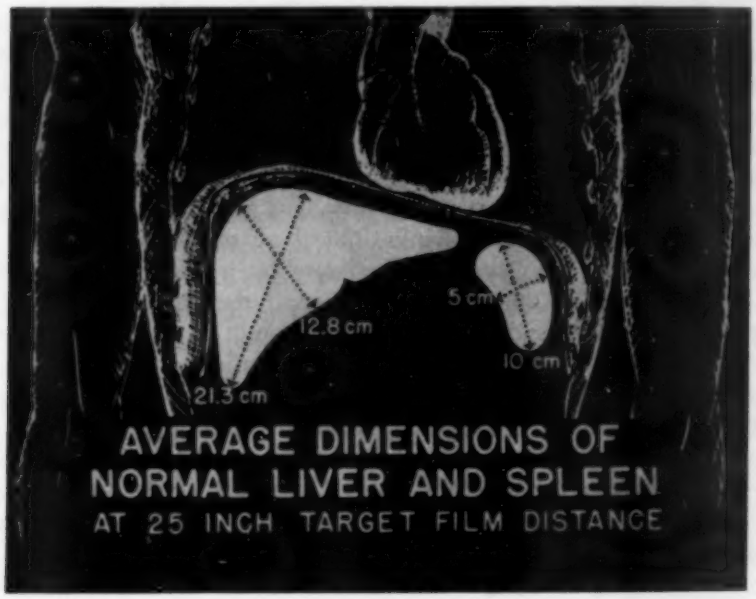
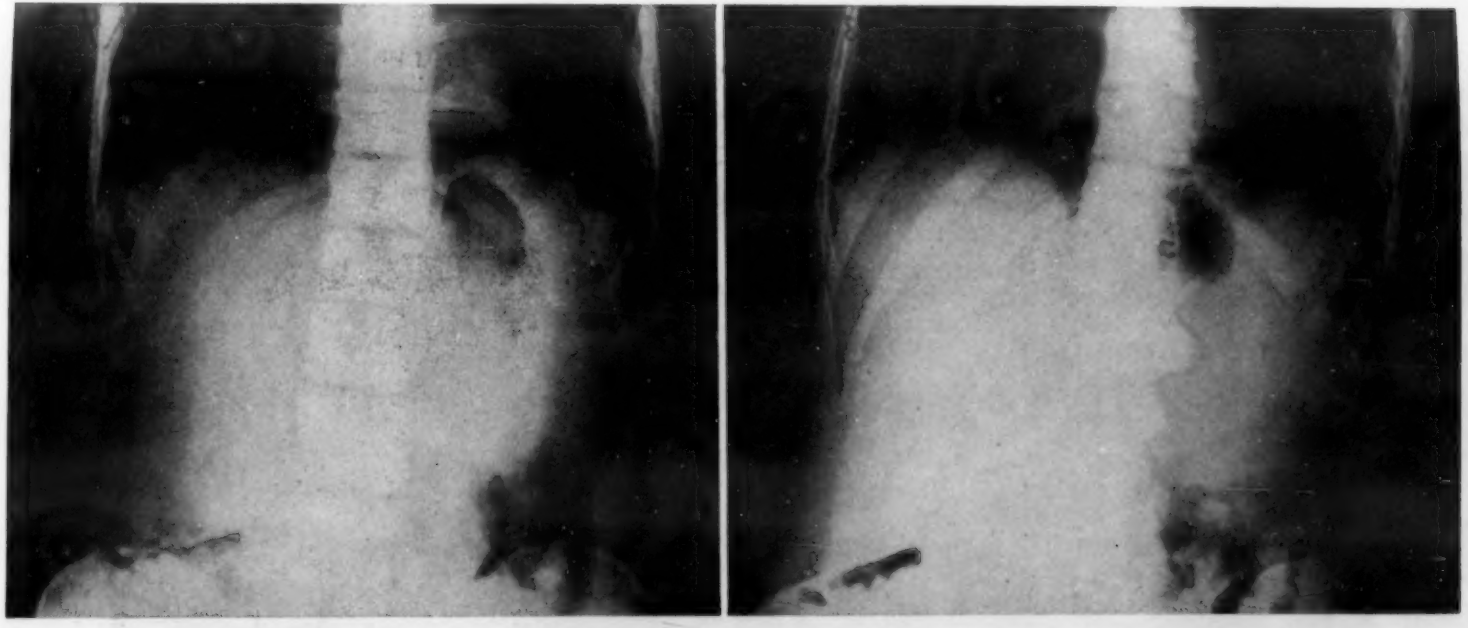


FIG. 1. (Adapted from Martin.[1]) Explanation in text.

The spleen is described in Gray's Anatomy as being situated between the fundus of the stomach and the diaphragm. Such a transversely lying spleen was observed by us in the majority of cases, but many spleens were observed to occupy a lateral and more vertical position between the body of the stomach and the lateral chest wall. This was also observed by Dell and Klinefelter, who found no constant relationship of the spleen to the diaphragm. We observed no change in position of these two types of spleens in the right lateral decubitus position, other than slight separation from the lateral chest wall (figure 3).

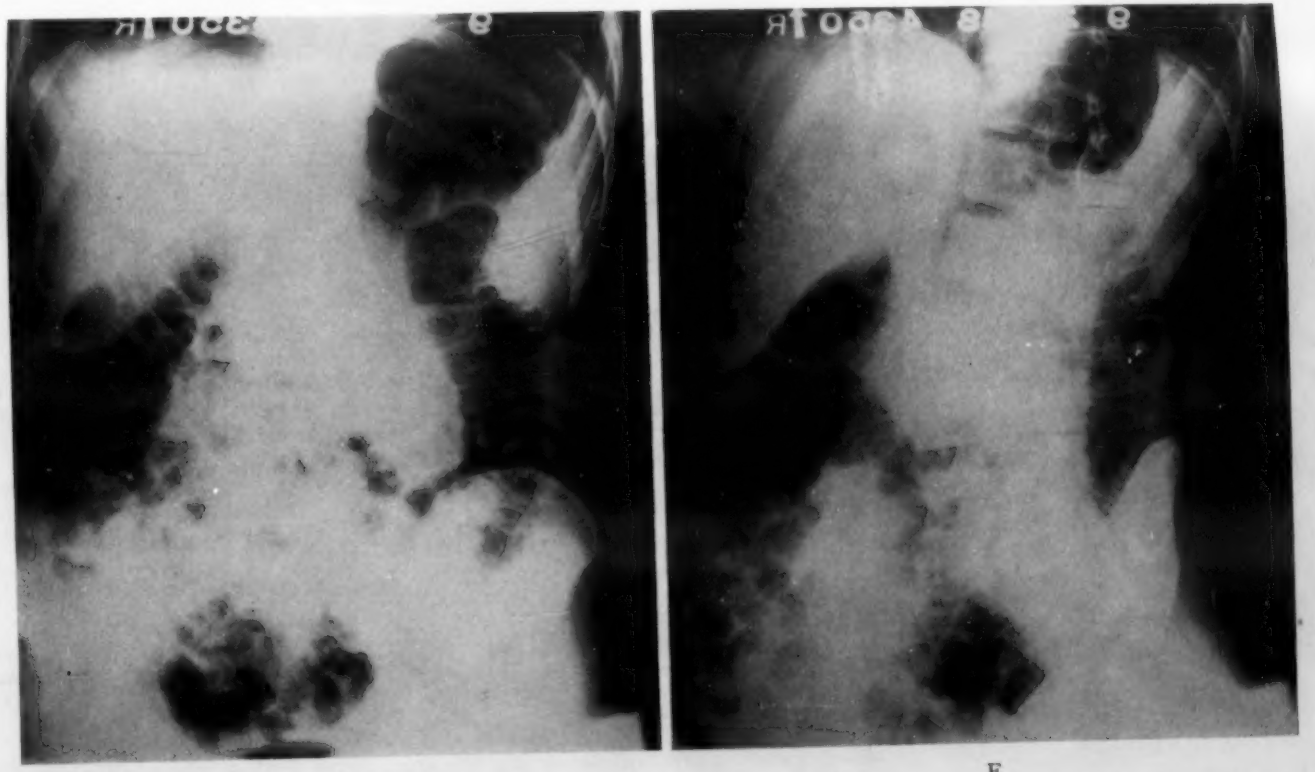


A B

FIG. 2. Serial liver-spleen visualizations in a patient with acute infectious mononucleosis. The patient had clinical, laboratory and needle biopsy findings of hepatitis, the biopsy specimen showing infiltration of the periportal zones of the liver by mononuclear cells. Clinical palpability of these organs corresponded to the visualized findings. A (postero-anterior view) and B (left anterior oblique view). Markedly enlarged liver and spleen are seen on August 25, at the height of illness.

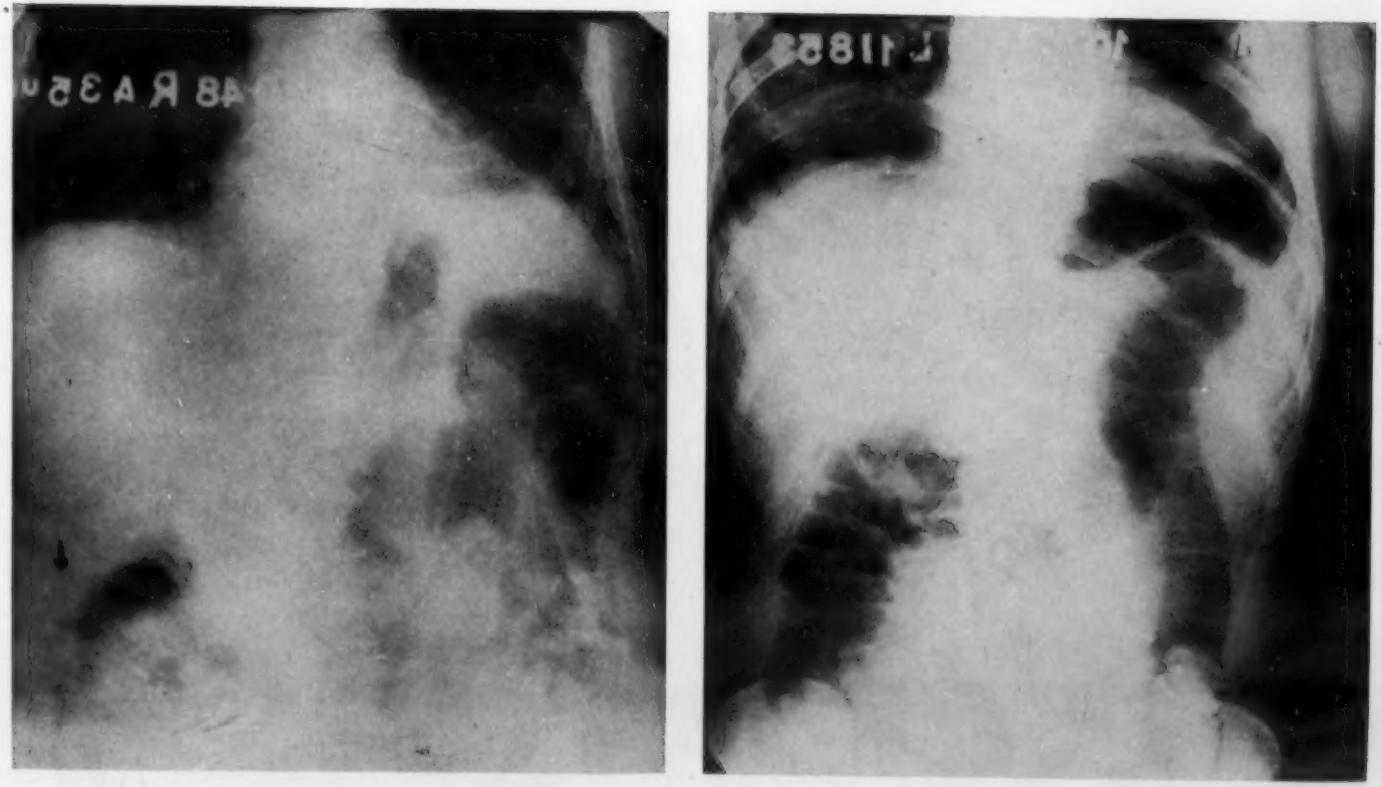
C D

FIG. 2. C (postero-anterior view) and D (left anterior oblique view). Moderate enlargement of both organs is still present on September 14, when the patient was clinically improved.



E F

FIG. 2. E (postero-anterior view) and F (left anterior oblique view). On September 29, at time of convalescence, the liver and spleen are of normal size.



A B

FIG. 3. Examples of horizontal and lateral positions of the spleen, as seen in the PA view. These positions are characteristic of the individual, and are not changed by respiration or change of posture. A. Moderate enlargement of the liver and a normal size transverse spleen are seen. The arrow points to a single rounded laminated gall stone visible within the liver shadow. The splenic flexure of the colon lies beneath the spleen. B. Normal size liver and spleen. The spleen is of the low-lying lateral type, which may be palpable in the absence of enlargement. The splenic flexure of the colon lies above and medial to the spleen.

Early in our study, we discarded measurement as a technic for determining liver and spleen size because of the conviction that physique and individual variability could not thus be adequately taken into consideration, and because the full length of these organs is not always visible. It is our practice to interpret their size as being small or normal, or slightly, moderately or greatly enlarged. Measurements may be of value, particularly in serial studies (figure 2). Shape and position of liver and spleen are also observed in reading the roentgenograms, and sometimes yield diagnostic clues.

Not infrequently, other findings of interest are noted in the films. Prominent among these have been calcifications within the spleen, liver, gall bladder, pancreas and kidneys. Outlines of the kidneys are usually easily discernible. On two occasions the gall bladder fundus was visualized at the liver edge, subsequently confirmed by cholecystography.

The visualization procedure occasionally has been of aid in the localization of abdominal tumors. In the case of one patient who complained of a phantom (disappearing) tumor in the right upper quadrant associated with pain and distress, colonic inflation resulted in reproduction of the tumor and symptoms. The films showed marked gaseous distention of the hepatic

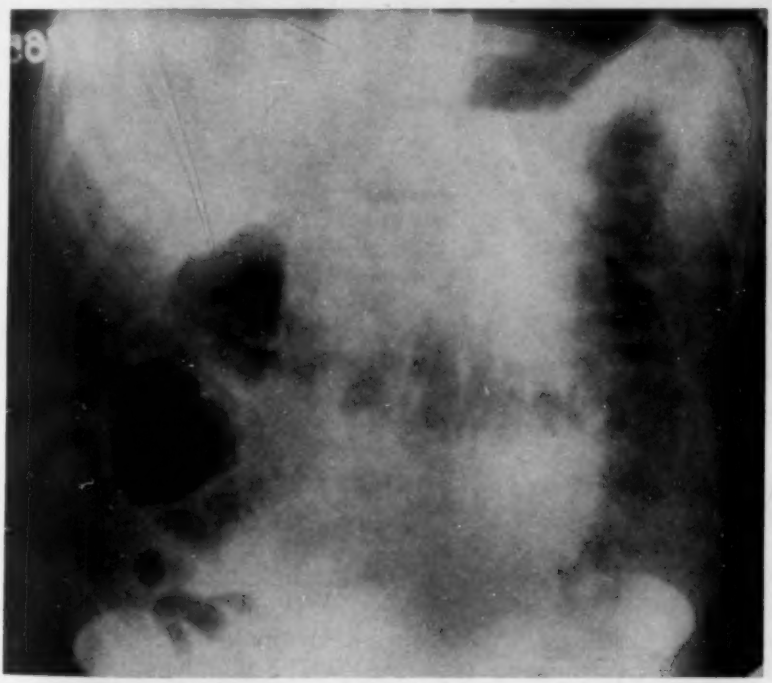


FIG. 4. PA view. The liver-spleen visualization is of diagnostic value in cases of obesity, in whom palpation may be difficult or impossible. Note the well delineated liver edge and spleen outline in a markedly obese individual. The marked thickness of the fatty layers of the abdominal wall is evident in the radiograph. Liver and spleen are of normal size.

flexure and ascending colon, secondary to kinking in the pelvis of a redundant transverse colon. This was subsequently confirmed by barium enema fluoroscopic study, which demonstrated the non-organic nature of the constriction (figure 7).

An attempt at correlation of clinical palpability of the liver and spleen with enlargement on roentgen visualization was abandoned, because many of our cases were referred for aid in evaluating questionable palpability. Nevertheless, it was evident that clinical palpability as a method of estimating liver and spleen enlargement was in error in a surprisingly high per cent.

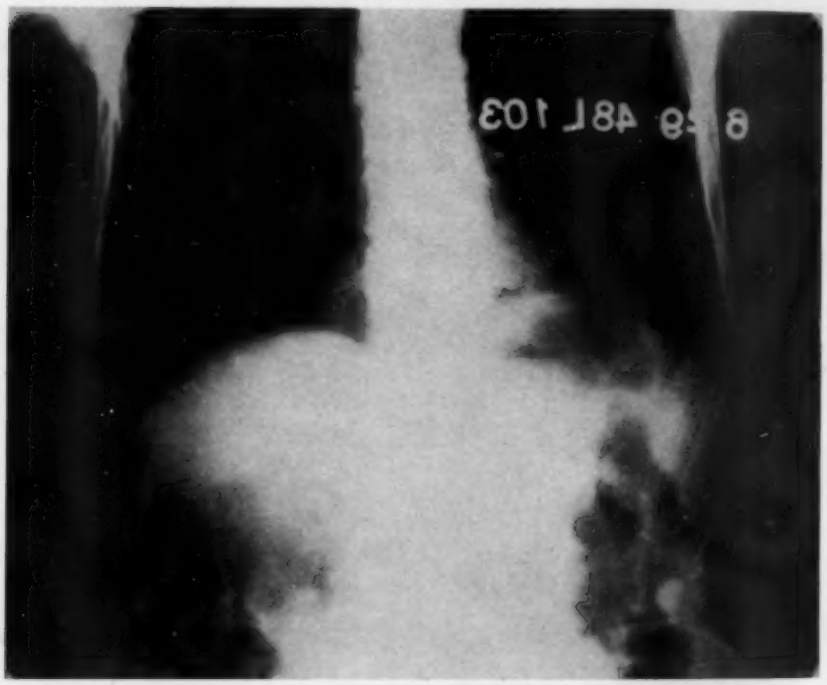
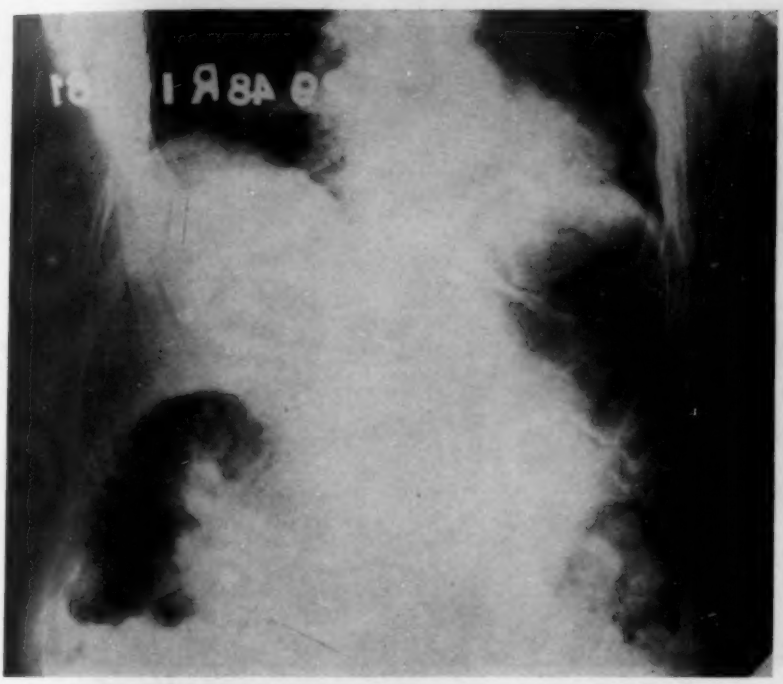


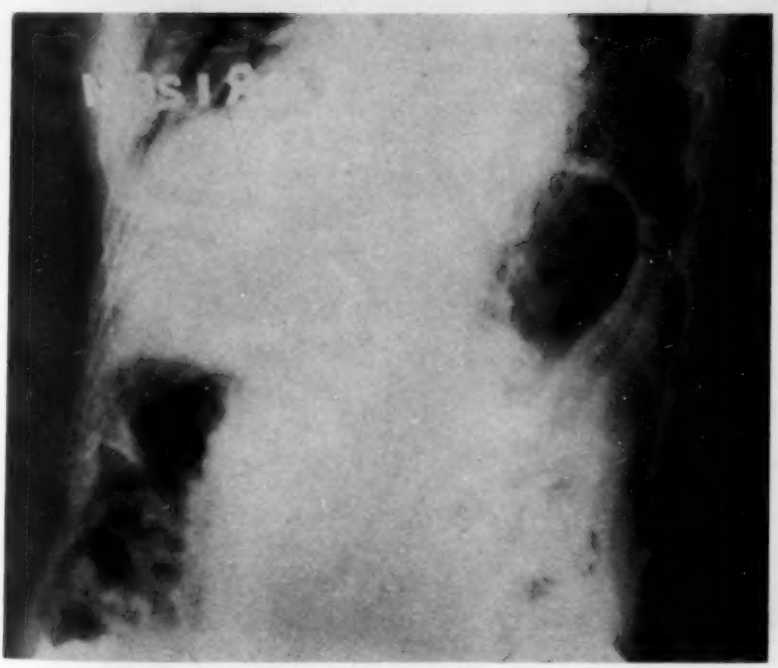
FIG. 5. PA view. This small liver was clinically palpable, due to displacement by emphysema. The spleen is also small.

Errors occurred in both directions, i.e., palpable organs were often not enlarged, and enlarged organs frequently were not palpable. The degree of development and tension of abdominal musculature, width of the costal angle, nutritional state, position of the diaphragm and other factors may account for this discrepancy. We have been impressed particularly by the high incidence of palpable livers depressed by the low diaphragms and wide costal angles of emphysema (figure 5). The high-lying transverse type of spleen may be enlarged, yet not extend below the costal margin, whereas the low-lying lateral spleen may be palpable when of normal size (figure 3).

Dell and Klinefelter [8] noted a similar lack of correlation between pal-



A



B

FIG. 6. A and B. **PA and oblique views of a splenectomized patient. Note the "vacant" left upper quadrant. The liver is of normal size.**

B

A

FIG. 7. A and B. PA views of a phantom tumor of the right upper quadrant reproduced by the colonic inflation of the visualization procedure. Gaseous distention of the proximal colon was secondary to kinking of a redundant transverse colon. Barium enema fluoroscopic examination confirmed the transient nature of the obstruction.

pability and visualization of spleen size when seen on flat films. Osgood and Habbe [9] found little difference in roentgen size of palpable and nonpalpable livers. Rives, Romano and Sandifer,[10] in a series of 41 cases of carcinoma of the pancreas, found only 16 enlarged livers at autopsy among 28 reported clinically palpable, and six enlarged livers among the 13 not clinically palpable. Ratnoff and Patek,[11] in a study of Laennec's cirrhosis, correlated clinical palpability of livers and spleens with size of the organs as observed at autopsy. They found 78 palpable livers to vary in weight from 695 to 5,100 gm. while 30 nonpalpable livers weighed 570 to 2,920 gm., "demonstrating only a rough correspondence between liver size and palpability." Forty-three palpable spleens ranged in weight from 180 to 1,700 gm.,

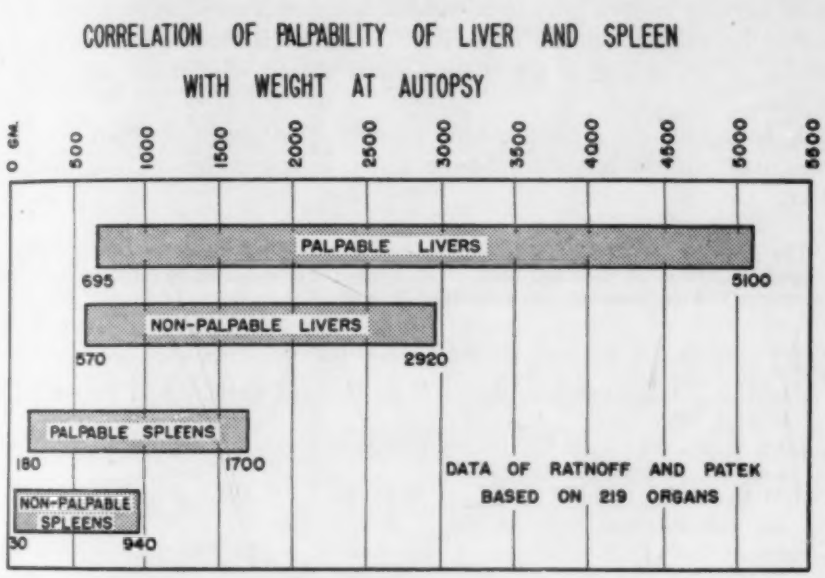


FIG. 8. The overlapping of the columns indicates the wide range of organ size in which palpation is unreliable for determination of the presence of enlargement.

while 68 nonpalpable spleens weighed 30 to 940 gm. These authors concluded that "a palpable spleen is much more likely to represent an enlarged spleen than a palpable liver is to represent an enlarged liver." It is apparent from their figures (see figure 8) that only huge organs (liver over 2,920 gm., and spleen over 940 gm.) could be reliably palpated, and that in many instances small organs were clinically palpable. The value of roentgen visualization for accurate determination of liver and spleen size is therefore evident.

COMMENT

Though this method of liver and spleen visualization was conceived independently, the author does not claim originality. A similar method was

suggested in 1914 by German authors,[12, 13] but was later abandoned in favor of pneumoperitoneum. Improvements in roentgen technics since that date, particularly the use of the Bucky grid, are responsible for the better radiographic visualization obtainable now, and obviate the fluoroscopic observation required by these early workers.

Summary

1. Available methods of roentgen visualization of the liver and spleen are reviewed briefly, and a simple gas contrast method of wide applicability is described.

2. Considerable variation in the normal position of the spleen was found, varying from a horizontal subdiaphragmatic position to a low lateral position between colon and chest wall. The horizontal spleen may not be palpable when enlarged, while the lateral spleen of normal size may be palpable.

3. In agreement with previous authors, this study revealed poor correlation of clinical palpability with actual enlargements of the liver and spleen.

The author gratefully acknowledges the aid and encouragement of Dr. Hans Lewin, roentgenologist, and his technical staff. The figures were prepared by Medical Illustration Laboratory, Winter Veterans Administration Hospital.

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CASE REPORTS

A CASE REPORT OF AN UNUSUAL LUNG ABSCESS DUE TO *CL. PERFRINGENS* (*B. WELCHI*)*

By Ralph F. Jacox, M.D., *Rochester, New York,* and Paul Dionne, M.D., *Montreal, Canada*

This case report concerns a study of a 30 year old woman who developed an acute pulmonary abscess from which a pure culture of *Cl. perfringens* was isolated. This circumstance is unique because of the rarity of this infective agent in pulmonary suppuration. Moreover, the presence of single bacterial species in purulent lung abscess fluid is of infrequent occurrence. Finally, the complete recovery of the patient from such an invasive, pathogenic organism is of particular interest.

Case Report

The patient, a 30 year old married female, suddenly developed an acute onset of severe right anterior chest pain six days before she was admitted to the Rochester Municipal Hospital on March 16, 1948. The chest pain was pleuritic in character and radiated into the right scapular area. Despite the pain the patient was able to continue her housework for three days, at which time she first became aware of fever and felt ill enough to go to bed. A physician was called who administered sulfadiazine, 1 gm. every four hours. One day before admission to the hospital, the patient developed a hacking cough which was productive of small amounts of white mucoid sputum. On the morning of admission to the hospital a small amount of bright red blood was observed in the sputum, which continued to be blood-streaked thereafter. In the same afternoon, the patient had several shaking chills.

There was no preceding history of choking on aspiration. No recent oral or dental surgery had been performed. The patient had noted a small reddened area on the right lateral malleolus several weeks before the onset of the present illness. This area had been tender, but had subsided within several days of the onset.

In 1936 the patient had spent five months in Ray Brook Tuberculosis Sanatorium because of pleurisy of the left lung. Subsequent yearly examinations by means of chest roentgenograms were entirely negative. The last film of the chest, taken in February, 1947, revealed no abnormalities.

Physical examination revealed a poorly nourished, sallow looking woman who had a temperature elevation to 39.2° C., pulse rate of 120/minute and respirations 38/minute. She appeared acutely ill, with shallow, rapid respirations and a cough which was productive of blood-streaked sputum. The only significant observations, aside from the evident acute illness, were limited to the abnormalities in the chest. Expansion of the rib cage was limited on the right side. The percussion note was dull on the right posteriorly and flat at the base and over the lateral chest wall. Tactile fremitus was decreased at the right base to the angle of the scapula. Breath

* Received for publication December 2, 1948.
From the Department of Medicine, University of Rochester, and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals, Rochester, New York.

sounds were diminished at the right base and bronchial in character in the mid and upper right lung. No râles were heard.

Laboratory examination revealed a white blood cell elevation to 33,050, of which 95 per cent were polymorphonuclear leukocytes with many stab forms. The urine was negative except for 1 plus albumin. A blood serologic test for syphilis was negative. A sputum culture revealed *Streptococcus viridans.* An inoculation of the sputum into a mouse was negative for presence of pneumococci. Two aerobic blood cultures were sterile after five days' incubation. Three Ziehl-Neelsen stained smears were negative for tubercle bacilli.

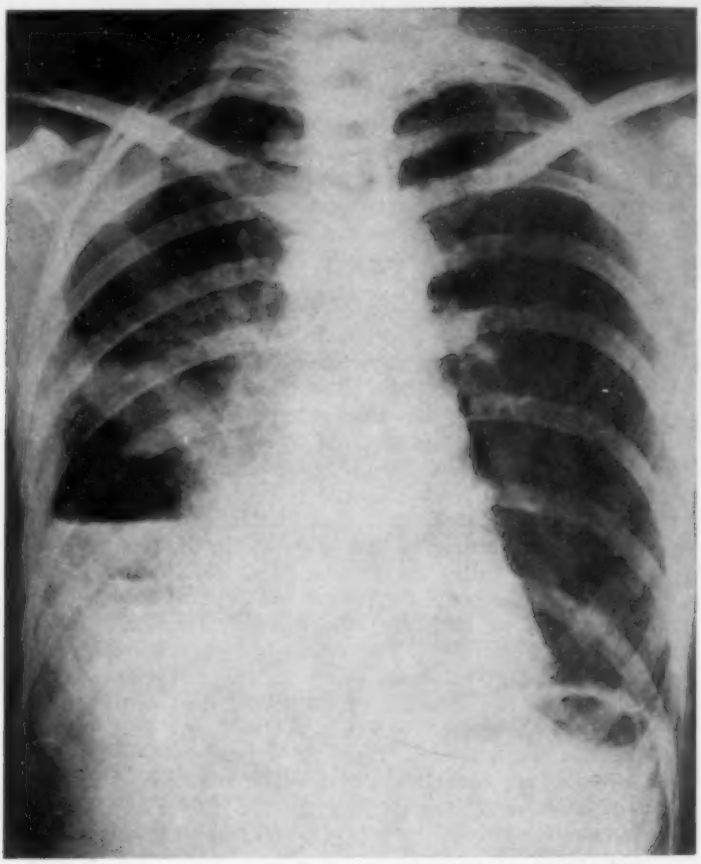

FIG. 1. Roentgenogram of lungs taken nine days after onset of illness. A large abscess cavity is present in the right lower lobe.

A chest roentgenogram taken the day of admission to the hospital showed a diffuse haziness of the entire right lung field. In the right midlung there was a narrow band of increased density extending from the hilum to the periphery. The left lung was negative. The roentgenogram was interpreted as showing a pneumonic pulmonary lesion associated with a small pleural effusion.

Course in Hospital: Intramuscular injections of penicillin were started (800,000 units a day) and continued for 11 days. For the next two days there appeared to be

little change in the course of the disease. The patient continued to have elevation of temperature between 39 and 40° C. Moderate toxicity persisted, but the patient developed no increased respiratory distress. Physical signs over the right lung showed no appreciable change from those present on admission. An attempt to aspirate a suspected pleural effusion was unsuccessful. On the third hospital day a roentgenogram of the lungs was repeated. This film revealed a large abscess in the right lower lung field (figure 1). On comparison with the preceding roentgenogram, it was apparent that rapid destruction of lung tissue had occurred in the three day interval.

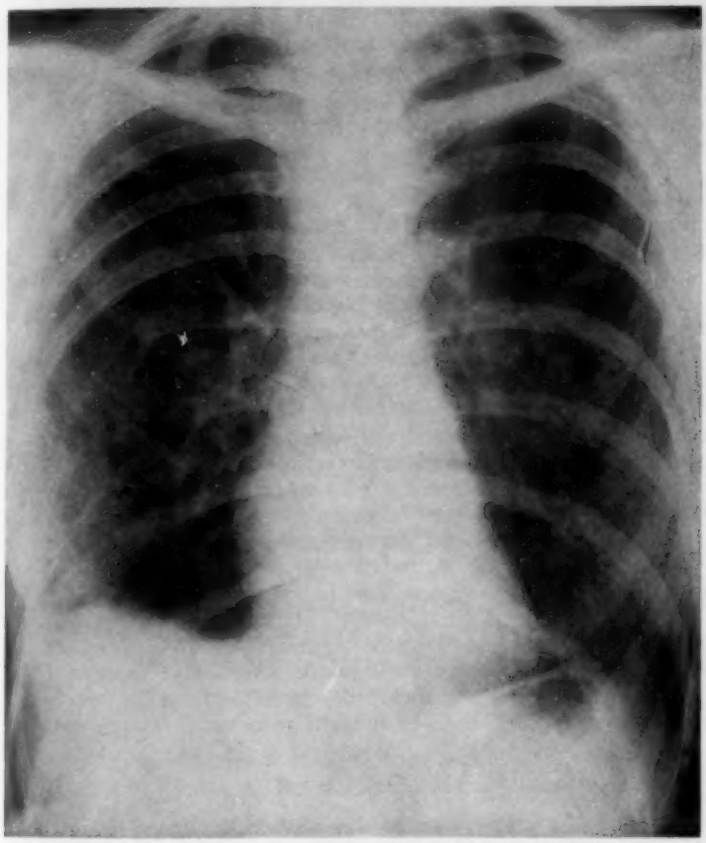

FIG. 2. Roentgenogram of lungs taken four months after operation. Complete healing of the abscess cavity has occurred. The right diaphragm is slightly elevated and adherent to the lateral chest wall. There is pleural thickening along the lateral chest wall on the right and increased markings in the right midlung field. The eighth and ninth ribs are partially resected.

The following day, surgical exploration of the abscess cavity was carried out under novocaine anesthesia. Incision was made in the posterior axillary line and the muscles were retracted to expose the seventh and the eighth ribs. Portions of these ribs were removed. By electric cautery, an incision was made directly into the abscess cavity. This was found to be 3 to 4 inches in diameter. It was partly

filled with a thin, sanguineous purulent material. The wall of the cavity was necrotic, soft and friable. No adherent material or pyogenic membrane was observed. The purulent material was aspirated for cultural study and the wound was partially closed after insertion of a folded cigarette drain.*

Immediately after the operation there was a fall in temperature to normal and the patient showed considerable clinical improvement. Serosanguineous material drained from the cavity for several days before a bronchopleural communication developed. Sixteen days after operation, the cavity was reëxplored. It was found to extend five inches into the chest but appeared clean and granulating. At this time, muscle approximation was carried out and a drain was re-inserted. A right phrenic crush was done.

Eight days after operation a thrombophlebitis developed in the right leg, in the same area in which the patient had noted a similar lesion several weeks before the onset of her illness.

Thirty-five days after the drainage of the lung abscess the patient was discharged from the hospital but returned for weekly examination in the chest clinic. The sinus in the chest wall continued to grow smaller and the bronchopleural fistula finally closed. A roentgenogram on August 12, 1948, revealed complete clearing of the lesion in the right lung field (figure 2).

Bacteriologic Examination of Abscess Fluid: Bacteriologic study of the abscess material was carried out within 30 minutes of the time of aspiration from the cavity. A gram stain revealed numerous white blood cells. In nearly every oil immersion field, 1 or 2 gram-positive rods, 6 to 8 microns in length, were seen. No sporulating forms were observed. Particular search was made for spirochetal organisms but none was found. No other bacterial types appeared to be present when several smears were examined.

Inoculations of the purulent material were made on rabbit blood agar plates and deep meat broth. An anaerobic culture was made on rabbit blood agar. Material was inoculated on Sabouraud's and Petroff's media. Forty-eight hours later, growth was observed only in the deep meat broth tubes. All of the several tubes inoculated revealed an abundant growth with stormy fermentation present. Gram stain of the broth revealed many gram-positive rods similar to those seen on direct smear of pus from the abscess. Aerobic and anaerobic subcultures revealed that the broth contained a single bacterial type. Subsequent inoculation of this organism and filtrates of it into guinea pigs established that the organism was *Cl. perfringens*. *Cl. perfringens* antitoxin afforded complete protection of guinea pigs inoculated with culture, whereas the animals not given antitoxin developed death in 18 hours with a typical gas gangrene. No tubercle bacilli or fungi were cultured from the abscess material.

Discussion

This patient had a primary acute lung abscess produced by infection with *Cl. perfringens*. A careful bacteriologic study failed to reveal any other associated organisms. Other reports of the bacteriology of lung abscess have, without exception, revealed a mixed flora of organisms.[1, 2, 3, 4, 5] It has not been possible, moreover, to discover any reference in the medical literature which describes *Cl. perfringens* as an etiologic agent in the production of pulmonary abscess.

In a series of cases studied by Cohen,[3] a saprophytic *Cl. cochlearum* was isolated from abscess fluid in a single instance. Several other aerobic bacteria were present in the same fluid. Letulle[7] states that *Cl. perfringens* is frequently

* Operation performed by Plimpton Guptill, M.D., Assistant Professor of Surgery, University of Rochester, School of Medicine and Dentistry.

isolated from lungs of patients dying with gangrene. However, it apparently was not isolated from patients with lung abscess. Glaser, et al.[6] report a patient who died of gangrene and lung abscess who had a postmortem culture of *Cl. perfringens,* but other bacteria were also isolated from this material.

It appears, therefore, that the present case had an unusual bacteriologic etiology of lung abscess, since *Cl. perfringens* was isolated in pure culture. The origin of the abscess in this patient may have been related to an infected embolus from a smouldering thrombophlebitis. It seems reasonable to assume that an infected embolus could produce a suitable environment in the lung, where anaerobic proliferation of *Cl. perfringens* could then take place. The rapid recovery of the patient after institution of surgical drainage and chemotherapy is of particular interest when one considers the invasive character of *Cl. perfringens* infections in the other parts of the body.

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THE SYNDROME OF COMPRESSION OF THE PULMONARY ARTERY BY A SYPHILITIC AORTIC ANEURYSM RESULTING IN CHRONIC COR PULMONALE, WITH REPORT OF A CASE *

By JULIUS R. PEARSON, M.D., F.A.C.P., *Miami Beach, Florida,* and E. STERLING NICHOL, M.D., F.A.C.P., *Miami, Florida*

SYPHILITIC aortic aneurysms appear with sufficient frequency to be easily recognizable. There is a multitude of complications occurring in combination with this entity, however, which present pictures that are less readily diagnosed. Among the most obscure is the syndrome produced by compression of the pulmonary artery by such an aneurysm, with the production of chronic cor pulmonale.

The rarity of this symptom complex is evidenced by the relatively few descriptions of it in the literature or in collections of specimens. Since 1811, 88 cases have been reported, as compared to the countless numbers of syphilitic aortic aneurysms that have been described since their earliest recognition. Antemortem

* Received for publication June 1, 1948.

designation has been especially trying because of the meagerness or multiplicity of findings in each case and because of the submergence of the exact pathologic state in the overall picture of catastrophic heart failure.

General Considerations

Aneurysms of the thoracic aorta may originate in the sinuses of Valsalva, the region just above the commissures, or further in the ascending arch, transverse arch, or descending portion of the arch. Some are congenital in origin, others are arteriosclerotic or mycotic, but most are acquired and are part of the total picture of syphilis. They may be saccular or diffuse,[6] multiple, and variously sized. In those involving the sinuses, there is a tendency to rupture before physical signs become apparent, unless aortic regurgitation occurs. When the aortic ring is dilated, the commissures show separation, aortic valvular insufficiency is presented as the main clinical feature, and the left ventricle enlarges and may eventually fail. When the aneurysm springs from the ascending portion of the arch, it usually assumes a large saccular form which may displace or compress adjacent structures such as the right atrium, right ventricle, conus arteriosus, coronary arteries, pulmonary artery, superior vena cava,[15] or left auricle.[4] There may be no symptoms, the heart may remain normal in size, and heart failure may not occur; but compression-dislocation or erosion phenomena may be seen, depending upon the site and direction of growth of the sac. Most of these arise from the convexity of the arch. In less frequent instances, the aneurysm arises from the concave surface of the ascending arch, and in order to compress and stenose the pulmonary artery the aneurysm must enlarge anteriorly and to the left. In this event, the right ventricle assumes the strain, hypertrophies and dilates, and inevitably fails, with the appearance of dyspnea, cyanosis, venous engorgement, hepatomegaly, ascites and peripheral edema. The pulmonary artery is obstructed, either by compression or erosion through its wall by the aortic aneurysm, with or without communication between the two vessels.[9]

Pulmonary artery compression by a syphilitic aortic aneurysm thus results in a cor pulmonale. The mechanism may be acute, with rapid right heart failure, or gradual, with recurrent bouts of right ventricular insufficiency. The process may go on unobtrusively for a long time and result in very little symptomatology, or it may make its dramatic appearance by rupturing through the wall of the pulmonary artery, producing an arterio-arterial fistula.[8] In any case, the patient ends his breathless life when his right heart can no longer maintain its adequacy.

Case Report

A 33 year old Negro male was admitted to the urologic service of the James M. Jackson Memorial Hospital on June 25, 1935, for incision and drainage of a periurethral abscess. In addition to the genital findings, his only other symptom was fever. He admitted having had gonorrhea four years previously but denied any primary or secondary luetic lesions. His blood showed a 2 plus Kahn test. Physical examination of the heart showed no enlargement or abnormality of sounds, although there was moderate tachycardia. Following the incision and drainage, he was started on bismuth and discharged from the hospital on July 13, 1935.

On March 6, 1936, he was readmitted, but to the cardiac service, with a history of dyspnea on slight effort and swelling in the epigastrium and right upper quadrant

for three weeks. There had been a moderately productive cough at the onset. He denied rheumatic fever, chorea or polyarthritis at any time in his life. He had no fever on this admission, and never did show any subsequent elevation of temperature, but his heart rate was between 90 and 100 per minute most of the time, and his respiratory rate was counted usually between 22 and 26 per minute.

Physical examination revealed moderate cervical fullness and pulsation of the veins, the trachea in midline without tug, impaired resonance over the left upper lobe posteriorly, and soft, crepitant râles bilaterally throughout. The heart apex was in the sixth interspace just outside the left midclavicular line; there was a faint systolic thrill over the mitral area; upper mediastinal dullness was increased two finger-breadths to the left of the left sternal border; a loud rough systolic murmur and a short diastolic murmur were heard in the second left interspace in the parasternal line and transmitted to the left axilla. The blood pressure was 150 mm. Hg systolic and 80 mm. diastolic; venous pressure was 10 cm. to 14 cm. on pressure over the liver.

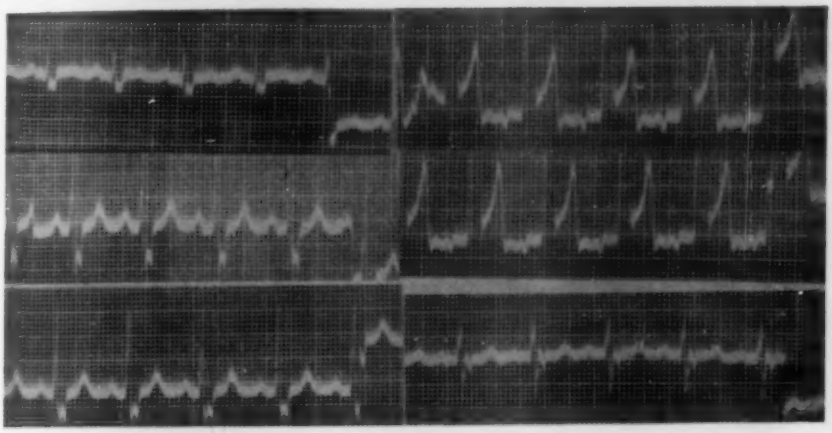

FIG. 1. Electrocardiogram on March 23, 1936, showing IV block with QRS 0.12 second.

The liver was firm and smooth three fingerbreadths below the right costal margin, and moderate ascites was present. The extremities showed no edema, clubbing or abnormal pulses.

Laboratory findings: Four plus Kahn test; urine, specific gravity 1.020, albumin heavy trace, microscopically red and white blood cells; complete blood count, normal, red cell sedimentation rate, 16 mm. per hour; non-protein-nitrogen 30 mg. per cent, creatinine 1.5 mg. per cent, chlorides 420 mg. per cent; sputum, negative for tubercle bacilli.

The electrocardiogram showed sinus tachycardia; PR 0.12 sec., QRS 0.12 sec., P upright in all leads; QRS upright in all leads with a deep, slurred S in all leads; ST isoelectric; T upright in all leads (figure 1).

Roentgenogram of the chest showed densities in both lung fields, pleural thickening at the right base, and a small collection of fluid in the right costophrenic angle. The heart showed a pulmonary conus abnormality which was interpreted as "aneurysm appears as likely as congenital heart disease"; fluoroscopically, no further help was obtained in more accurately describing the abnormality (figure 2).

Course: There was rapid clearing of pulmonary signs on a regime of bedrest, potassium iodide, bismuth-sodium-tartrate, digitalis and low ionic diet. The patient was discharged from the hospital on March 30, 1936, and enrolled as a patient in the

cardiac out-patient department, where he was followed at weekly intervals, with 12 subsequent hospitalizations, for the next four and one-half years. On each of these many readmissions, the chief complaint was always an increasing amount of dyspnea, ankle edema, abdominal fullness and distress, and cough, with gradually decreasing benefit from rest, diuretics and digitalis. On one admission, on July 14, 1937, he told of small, recurring hemoptyses, and on his final admission on October 25, 1940, he also complained of precordial pain and soreness.

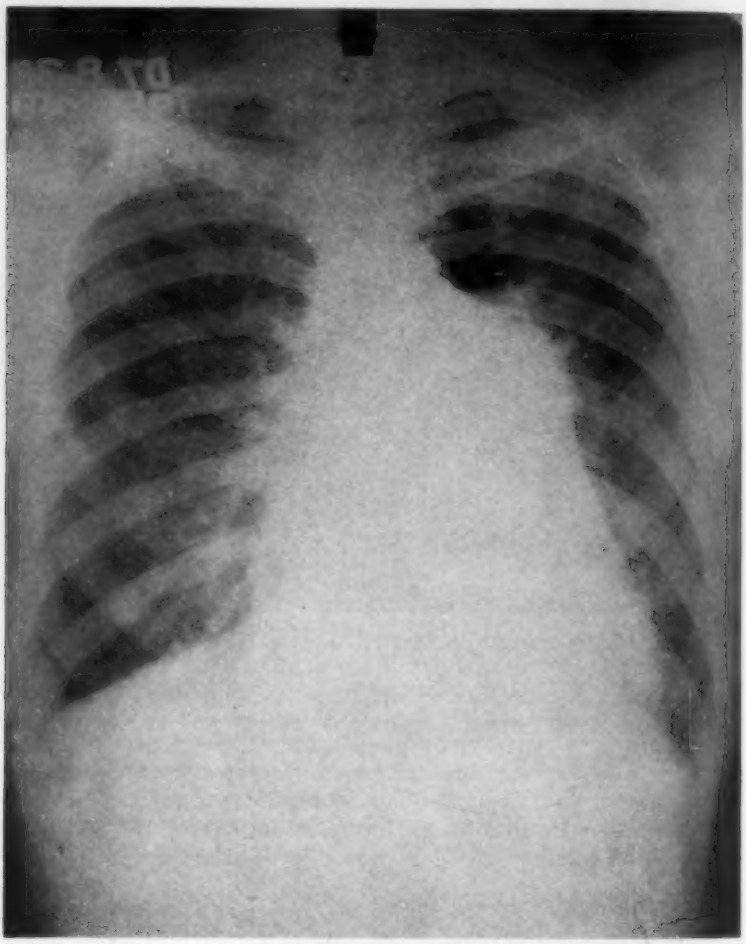

FIG. 2. Roentgenogram of the chest with findings similar to those seen on admission to Cardiac Service in March 1936, showing pulmonary conus abnormality which suggested "aneurysm" or "congenital heart."

The findings throughout these years were mainly the same, with increased venous pressure, pulmonary congestion, hepatomegaly, ascites and peripheral edema. The cardiac signs varied considerably. The apex beat was found progressively lateral from the point in the original description. Percussion outlined the increased cardiac dullness to both the left and the right. The thrill remained ever-present, but in

various positions over the entire precordium. Murmurs of every description were heard over each orifice during both phases of the cardiac cycle.

As to the rate and rhythm, there was always a tachycardia, often associated with a systolic gallop, ectopic beats and, finally, an irregular rhythm with pulsus bigeminus. It is to be remembered that the patient was on digitalis during each of his numerous hospital admissions after the first, and also intermittently during his intervals at home.

His blood pressure showed numerous fluctuations between 150–100/80–50 mm. Hg, and on his final admission it was 160/40–20 mm. Hg.

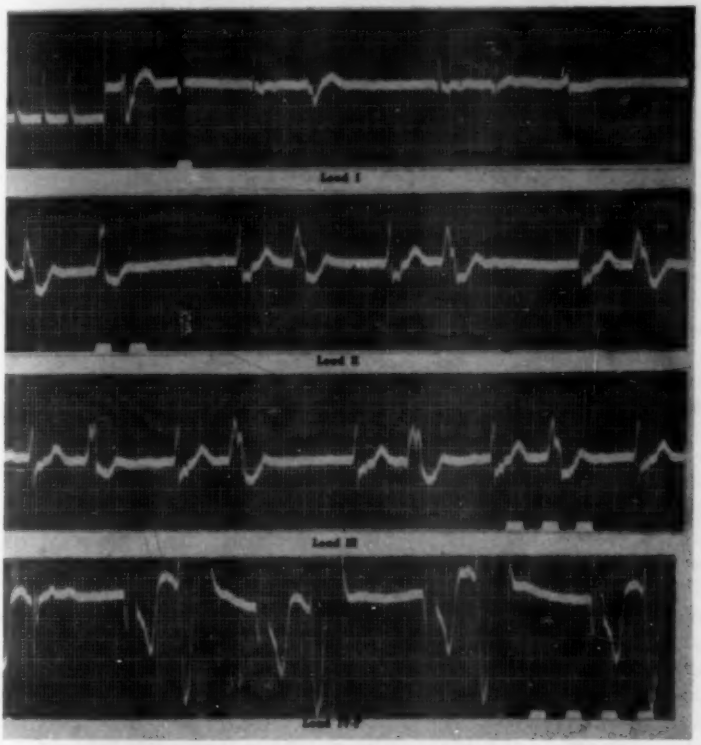

FIG. 3. Electrocardiogram showing persistent IV block, ventricular ectopic beats and alternating premature contractions producing bigeminy.

His venous pressure at first was 10 cm. to 14 cm. on hepatic pressure, and subsequently showed 24 cm. to 27 cm. One circulation time, on his seventh admission, showed 42 seconds for the peripheral circuit with calcium, and 12 seconds through the pulmonary circuit with ether. Throughout his entire course, his blood count and chemistry remained within normal limits, but his blood Kahn varied irregularly between 4 plus and 0. His urinalysis showed a specific gravity up to 1.020 on individual specimens or in concentration tests, albumin from 4 plus to faint trace, various hyalin and granular casts, and red and white blood cells.

Roentgenologic studies and fluoroscopy with barium at intervals showed various areas of increased densities in both lung fields, which eventually cleared, and also showed small collections of fluid in the right costophrenic angle, which likewise

cleared. Various descriptions of the cardiovascular shadows are given: gradually increasing transverse cardiac measurements, posterior displacement of the esophagus, diminished pulsation in the left ventricle and increased pulsation in the right ventricle, and marked enlargement of the pulmonary artery and conus with calcification in this region, which in the lateral view seemed to extend mostly anteriorly and superiorly above the right ventricle. These bizarre findings were interpreted as pulmonary artery aneurysm, localized dilatation of the right ventricle with calcification within its walls, or congenital heart disease. One clinical observer's impression was that we were dealing with a congenital pulmonary stenosis (figure 3).

The electrocardiographic findings presented persistent evidence of intraventricular block without axis deviation. On occasions, ventricular ectopic beats were noticed, and just before his last admission to the hospital his tracings showed alternating premature contractions and prolonged PR intervals, which were attributed to digitalis intoxication and which clinically produced pulsus bigeminus.

On his final admission, on October 25, 1940, the picture again was that of marked right and left heart failure. On the following day he became restless and nauseated, and vomited several times. On his third hospital day, following a trip to the bathroom, he went suddenly into acute pulmonary edema and died.

Autopsy findings: The following are the pertinent findings reported: Approximately 1,500 c.c. of straw-colored fluid were found in the abdominal cavity. There were many adhesions over the right lung. Both lungs, especially the left, showed numerous bullous-like formations, filled with air (1 to 4 cm. in diameter) and intervening induration. On compression, a foamy white fluid was expressed.

The pericardial cavity contained a normal amount of straw-colored fluid. The heart was tremendously enlarged, and both ventricles were markedly hypertrophied and dilated. The right ventricle was relatively much larger than the left. The surface of most of the heart was smooth and glistening, with the exception of a few "milk spots" and numerous old subepicardial hemorrhages. The surface corresponding to the left margin of the left ventricle, including the entire lower one-fourth of the left ventricle, was rough and showed a very fine, fibrinous membrane. The circumference of the base of the heart measured about 28 cm. The anterior sulcus, from crown to apex, on the anterior aspect measured 14.5 cm.; on the posterior aspect, 10.5 cm. The interventricular septum, from membranous septum to the apex, measured about 10 cm. The wall of the left ventricle measured between 1.8 and 2.0 cm., while that of the right ventricle measured between 9 and 10 mm. The wall of the left auricle measured about 2 mm.; the right auricle, about 3 mm. The foramen ovale was closed. The circumference of the mitral ostium measured 8 cm.; the leaflets were shorter than usual, measuring 5 to 8 mm., but the cusps and chordae tendineae were fine and delicate. The aortic ostium measured 7 cm.; the pulmonary ostium, 4.5 cm.; the tricuspid ostium, 13.5 cm. The cusps of the aortic valves measured 1 cm.; between the right and left anterior cusps there was an interval measuring 3 mm. Just above the aortic valves there was a large orifice leading to a saccular aneurysm (figure 4). The diameter of the aneurysm measured 10 cm.; its walls consisted of fibrous tissue, cholesterol and calcified laminae. The aorta itself was partly calcified. The aneurysmal sac extended toward the left and diffusely compressed the pulmonary artery. The latter had a small orifice with a bulging, firm, ridge-like formation toward the right ventricle. The cusps of the pulmonary valve were very delicate, but the right anterior cusp was only rudimentarily present; only its lateral part was noticeable, and measured about 3 mm., while the other cusps measured about 8 mm. The myocardium was firm in consistency and showed numerous fibrotic areas. The coronary arteries were patent grossly.

The liver weighed 1,550 gm.; the spleen, 450 gm.; the left kidney, 230 gm., the right, 200 gm.

Microscopy: Sections from all four chambers of the heart showed hypertrophy with large muscle fibers and large nuclei, and scarring. The coronary arteries showed collagenous thickening of the intima, with dissociation and splitting of the elastic fibers and replacement with connective tissue. The pulmonary artery and its main branches showed intimal and medial thickening and edema, with marked narrowing of the vessel lumen in several instances, and interruption and breaking of the internal elastic fibers. Sections of the lungs showed signs of emphysema and collapse, plus marked accumulations of bright golden brown hemosiderin pigment (heart failure

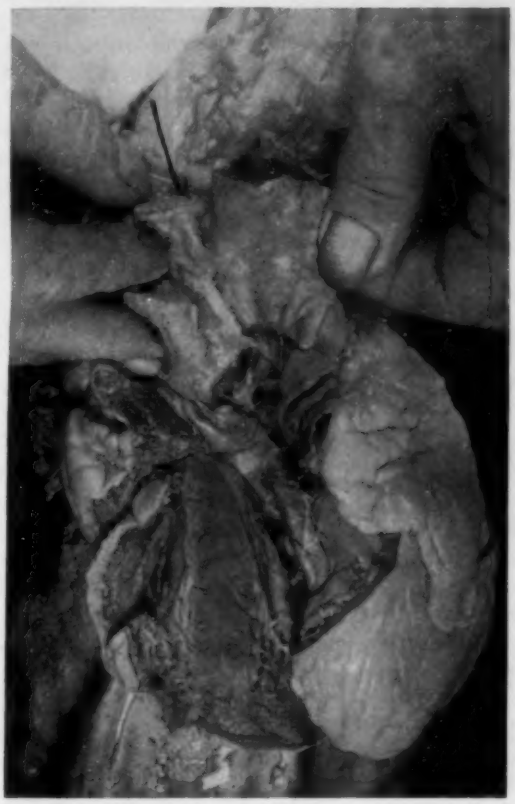

FIG. 4. Orifice in aorta leading into saccular aneurysm, thickened left ventricular wall, and calcified aorta.

cells). Liver sections showed thickening and hyalinization of Glisson's capsule, with strands of connective tissue extending into the depths of the liver, where they united with strands of connective tissue forming extensive scars. This process separated and formed the large packages of liver tissue often seen in healed syphilis of this organ or after extensive hepatitis, the liver being transformed into the so-called "nodular hyperplasia." No vascular changes were noted in the liver. Sections of the kidneys showed glomerular congestion and some exudate into the Bowman capsules. The tubules showed a marked degree of hydropic swelling. Arteriosclerotic changes, elastic splitting, and replacement with connective tissue were noted.

The anatomical diagnosis was as follows: saccular aneurysm of the ascending

aorta above the valves, with compression of the pulmonary artery; aortic insufficiency; pulmonary insufficiency due to lack of one pulmonary valve; functional pulmonary stenosis; functional tricuspid insufficiency; pericarditis; syphilitic mesaortitis; hypertrophy and myofibrosis of the heart and dilatation of all four chambers; pulmonary emphysema and edema, and nodular hyperplasia of the liver.

Discussion

The various syndromes produced by syphilitic aneurysm have been seen often enough to pose no great problems of diagnosis. The one herein discussed is an intermediate phase in a relatively rare symptom complex. Its recognition is defied by unusual findings which, in most instances, give no indication of the true anatomic complications. The complexity produced by the cardiac signs per se probably serves to confuse the diagnosis. There is none which is pathognomonic of the syndrome. None may even be evident early, as in our case, or as described by Brill and Jones.[1] The murmurs, when they do appear, may be over the apex, pulmonic or aortic areas, individually or in combination, with or without associated thrills, and with or without transmission. The most important early adventitious sounds, however, are those audible at the base and left sternal border, where the systolic and diastolic murmurs and oft-associated systolic thrill may resemble those of a patent ductus arteriosus. Later, as heart failure ensues, any sign is possible and makes for equivocation.

Roentgenographic findings are not always of help in the diagnosis. The evidence of enlargement of the right heart and of the pulmonary artery and conus is not sufficiently specific, nor is it as usual as the syndrome itself. However, when calcification of the mass is also seen, especially in a comparatively young luetic adult, the existence of this rare anatomic diagnosis should be considered. Kymography and angiocardiography are useful corroborative procedures.

Electrocardiographic reports in this uncommon entity have usually indicated the features of a right-sided strain, characteristic of the cor pulmonale syndrome. Garvin and Siegel [6] report two cases with normal mechanism and right axis deviation (in one of which there was notching of the QRS in all leads). The case of Eichler and Heller [4] shows sinus rhythm, tachycardia and prolonged PR interval, while the case of Brill and Jones [1] shows progressively increasing right axis deviation and strain. Our case is therefore unique, inasmuch as intraventricular block existed throughout the entire course. This may have been the result of a fibrotic area (of which many were found microscopically) which interfered with conduction, and the block did not change even under the effect of digitalis saturation.

A résumé of the diagnostic problems includes various differentials. Most of the cases of the syndrome so far described have been seen in relatively young adults. Syphilis has been present, acknowledged in the history or found in the serologic tests. Symptoms of dyspnea, cyanosis, hepatomegaly, increased venous pressure, ascites and peripheral edema are not pathognomonic of the syndrome per se, but do point to right heart failure. And if there are signs of aortic enlargement at the cardiac base, a double murmur and systolic thrill over the pulmonic area, roentgenographic evidence of enlargement of the right heart, pulmonary artery and conus, and electrocardiographic right axis deviation, the syndrome should be considered. Rheumatic heart disease with mitral stenosis involves both the right and left heart, but the left auricle is enlarged. Congenital communications between the aorta and pulmonary artery, such as patent ductus

arteriosus or arterial septal defect, usually manifest themselves early in life; their murmurs are more harsh and machinery-like; the left auricle is enlarged, and fluoroscopically there is a "hilar dance." Interauricular septal defects do not produce the same murmur as arterial septal defect but are also evident from birth, and the heart shadow tends to show a narrow hypoplastic aorta and an extremely dilated pulmonary arterial tree.[13] Pulmonary endarteritis obliterans produces right ventricular failure, but the deep cyanosis of these "black cardiacs" is characteristic. Sickle cell anemia is recognizable by hematologic study. A mediastinal neoplasm does not usually show a fluoroscopically expansile pulsation unless it is in close contact with the aorta. In the latter case, the pulsation may be transmitted to the mass. Careful fluoroscopy may reveal that the tumor is not continuous with the aorta and may show variations in densities of the two structures. Beriberi produces signs of right ventricular failure, but depends on a history of dietary deficiency and usually is associated with a relatively rapid circulation time.[5] Pulmonary artery aneurysm is also a rare entity that produces a prominent pulmonary hypertension, pulmonary conus, and a harsh systolic murmur and thrill over the pulmonic area.[7] These cases are usually encountered in the presence of other congenital anomalies, of which the patent ductus arteriosus is the most common. Boyd and McGavack [2] believe that this syndrome is dependent on the pulmonary hypertension plus an additional lesion, such as superimposed infection or atheromatosis, which weaken the arterial wall. In any event, as Deterling and Clagett [16] point out, the most diagnostic feature of pulmonary aneurysm is the presence of a discrete, pulsating hilar mass, separate from the aortic shadow. These authors, and Robb and Steinberg,[17] stress the value of roentgenologic and angiocardiographic methods in such cases. In cor pulmonale due to chronic pulmonary disease, such as chronic emphysema, long-standing asthma, pulmonary fibrosis, etc., Spain and Handler [18] show that the pulmonary picture is predominant, and the cardiac signs, acute or chronic, may not appear until near the end.

Summary

The syndrome of compression of the pulmonary artery by a syphilitic aneurysm arising from the ascending aorta is rarely encountered and is difficult to diagnose.

Cor pulmonale makes up the greatest part of the clinical picture. This may be acute or chronic. In the case presented, it lasted for more than four years.

The usual ending for this intermediate syndrome is the rupture of the aneurysm into the pulmonary artery, producing a fatal arterio-arterial fistula, but, as in this case, death from right heart failure may occur before the erosion takes place.

The signs are not particularly diagnostic, but the murmurs and thrill are usually most pronounced in the second or third interspace to the left of the sternum.

Roentgenographic findings are those of an enlarged right ventricle, pulmonary artery and conus.

The electrocardiographic findings are usually those of progressively increasing right axis deviation. In the case herein presented, there was evidence of intraventricular block.

Diagnosis of the syndrome should be kept in mind in all syphilitics who present evidence of embarrassment of the right heart, a systolic and diastolic murmur, and a systolic thrill over the pulmonic area, and who present roentgenographic findings of enlargement of the right ventricle, pulmonary artery and conus.

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HYPERTROPHIC PYLORIC STENOSIS IN ADULTS*

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HYPERTROPHIC pyloric stenosis in infants is a common and well established entity. Hypertrophic pyloric stenosis in adults is achieving increasing publicity as reports begin to trickle into the literature. Over 100 cases thus far reviewed

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stress its more than academic importance. The importance of bringing to the attention of clinicians and roentgenologists another condition of differential significance in the difficult pyloric segment, justifies the addition of two more cases to the literature.

Historic

The first note of an adult case of hypertrophic pyloric musculature is found in the autopsy report of a 72 year old woman by Jean Cruveilhier.[1] A long interval followed before the report of the pathologic material on 31 autopsies by R. Maier[2] in 1885. In all his cases, marked dilatation of the stomach was present. Maylard[3] in 1904 reported seven cases of pyloric obstruction, of which only two were associated with vomiting since birth and of which the majority had histories compatible with duodenal ulcer and secondary stenosis. The most extensive series was that reported by B. R. Kirklin and M. T. Harris,[4] who presented the roentgen aspects of 81 cases and who proffered what they thought to be a distinctive roentgen-ray sign of this disease. Subsequent discussion will show that this finding is not always present nor is it characteristic when present. Surveys by Judd et al.,[5] Horton,[6] Wakefield,[7] Berk and Dunlap,[8] and Katz[9] have brought the literature of this condition up to date.

Etiology

The etiology of pyloric stenosis in adults is not clearly defined. A few gastroenterologists favor the congenital origin of this disease. The presence of symptoms from infancy is strongly suggestive. However, this clinical picture is very uncommon. Crohn[10] in 1928 stated that there were very few cases acceptable as of congenital origin. It is tenable that subclinical pyloric stenosis may have been present in infancy and that, throughout the years under repeated stress, symptoms became manifest first in adult life. Another small group of cases have their complaints appear first in adult life, and in this group there is no other demonstrable disease at the pylorus. Ulcer may have been present and healed. By far the majority of cases are noted clinically in adult life associated with gastric ulcers, duodenal ulcers, gastritis or some other more remote gastrointestinal diseases. Since gastric ulceration and inflammatory changes often occur after long standing pyloric stenosis, it is difficult in this group to postulate whether the pyloric stenosis is primary or secondary. Horton[6] suggested an autonomic imbalance between constrictor and dilator muscle fibers with a hypervagotonic preponderance as of etiologic significance. Allergy, endocrine disturbance and vitamin deficiency all have their adherents. Berk and Dunlap[8] have added the modern touch of psychosomatic factors and emotional distress as being significant. Up to the present it can be stated that: (1) no etiology has been established; (2) the congenital form with symptoms present since infancy is relatively rare; (3) the adult form is usually associated with ulcerations and inflammatory changes in the stomach, and (4) a few cases of the adult form have no associated disease present in the stomach.

Pathology

The primary pathologic change is hypertrophy as well as hyperplasia of the circular muscle of the pylorus. This often becomes two to three times its normal size. In some cases, the longitudinal muscle may also be involved. There may

be hypertrophy of all the layers of the stomach. With increasing stenosis there may be varying degrees of gastric dilatation, but obstruction is rarely complete. The mucosa and submucosa may be hyperemic and edematous. There is occasionally lymphoid hyperplasia. Superficial as well as deep ulcers and inflammatory changes are often found.

Symptomatology

There is no characteristic symptomatology. The majority of cases occur in the male. Most symptoms are a reflection of the degree of stenosis and associated secondary gastric changes. In the congenital as well as the adult form, varying degrees of vomiting of the retentive type are outstanding. There may be nausea, vague inconstant abdominal pain, constipation, weakness and weight loss present. The pattern of pain is usually a reflection of either associated ulcer or gastritis. Anorexia and early satiety are occasionally present. When vomiting occurs, undigested food is often present but large amounts of bile are uncommon.

Diagnosis

Clinically as well as roentgenologically it is impossible to make a definite and certain preoperative diagnosis. The roentgen-ray appearance of an elongated rigid and fixed pyloric canal with a narrow concentric lumen is not characteristic. The addition of Kirklin's [4] sign, of a smooth crescent invaginating the base of the bulb, was not present in either of my cases, and from a survey of the literature this experience is not unusual. At least it is not present often enough to be characteristic and, when present, has been found in conditions other than hypertrophic pyloric stenosis. The clinical findings of a brief ulcer-like history with signs of pyloric obstruction may point to neoplasm or ulcer as well as to hypertrophic pyloric stenosis. Gastric analysis and stool examinations as well as gastroscopic studies are of limited value.

The number of disorders which clinically and roentgenologically need to be differentiated is sufficiently large to invalidate any certainty of diagnosis. I have seen or read of similar roentgen appearance in carcinoma of the stomach, or carcinoma of the pancreas invading the stomach, in pyloric ulcer with secondary stenosis, giant rugae, hypertrophic gastritis, annular pancreas, antral spasm, prolapse of the gastric mucosa, in lues and in benign tumors of the stomach. The galaxy of conditions producing this pattern makes differential diagnosis impossible. Since medical treatment is inadequate in many of these conditions, especially when varying degrees of gastric dilatation and stenosis are present, and since neoplasm cannot be excluded, surgical exploration is deemed advisable. The only sure diagnosis is microscopic tissue diagnosis. The surgery to be followed will depend upon what is found at exploration. Should hypertrophic pyloric stenosis be proved, gastroenterostomy in the presence of hypochlorhydria, or gastric resection is desirable.

Case Reports

Case 1. The patient was a 59 year old white male whose chief complaint was that of vague epigastric distress associated with early satiety and fullness. There were periodic bouts of vomiting of many years' duration. The vomit was retentive in character, containing gross food and little bile. The past history was irrelevant.

The physical examination revealed a thin but well preserved male in no apparent distress. The only positive finding was a gastric succussion splash six hours after the last meal. The laboratory data included a normal urine; hemoglobin 94 per cent; red blood count 4,430,000; white blood count 8,600, with a normal differential. Three stools were negative for occult blood. The gastric analysis revealed a fasting residue of 150 c.c., with 30 c.c. of solid residue. There was a grade II hyperacidity, with

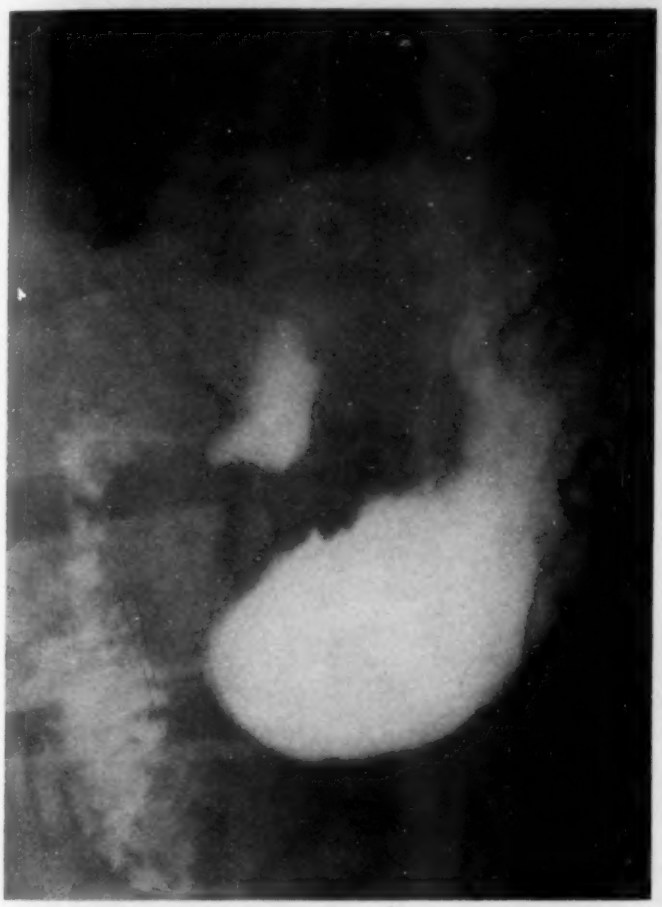

FIG. 1. *Case 1.* Note the elongated, narrow pyloric canal. There is a suggestion of a slight indentation in the base of the cap. The larger gastric ulcer is not seen in this view but a superficial ulceration is seen on the lesser curvature side in the antrum.

free acid rising to 85 units on a fractional analysis. A gastrointestinal series revealed a slightly dilated stomach with an elongated narrow pyloric canal. There was a questionable ulceration in the pyloric canal and a larger gastric ulcer above the re-entrant angle high on the lesser curvature.

Gastroscopy revealed the presence of the gastric ulcer on the lesser curvature with characteristics of benignity. A mild hypertrophic gastritis was present in the antrum. Because of the persistent narrowing and elongation of the pyloric canal

and because of the inability to exclude a neoplasm, surgery was performed by Dr. Charles Robbins at the Newark Beth Israel Hospital and resection done.

The pathologic report was that of a subacute diffuse gastritis, with a benign ulcer on the lesser curvature of the stomach and several small ulcers along the lesser curvature. There was a marked hypertrophy of the circular muscles of the pylorus associated with narrowing of the pyloric canal.

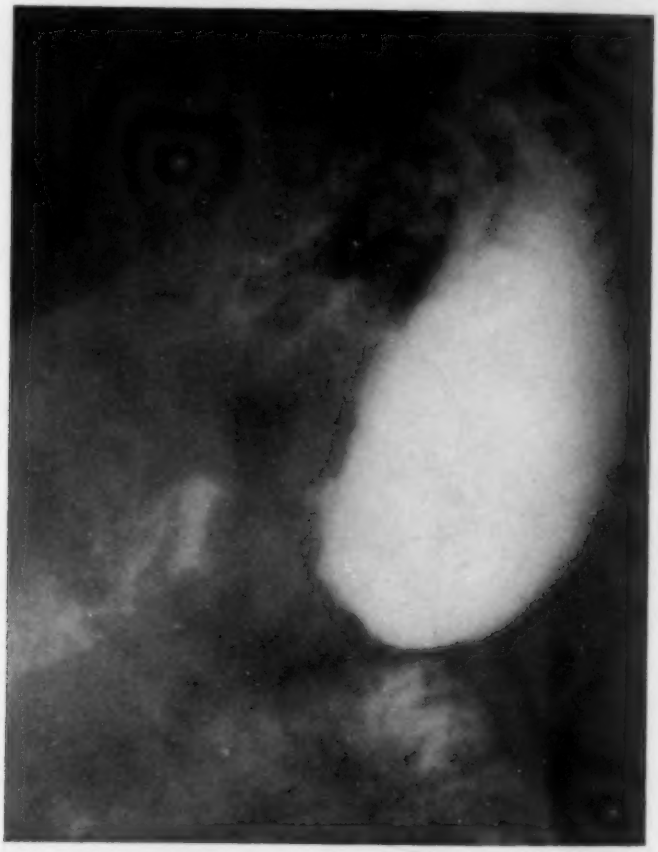

FIG. 2. *Case 2.* Note the persistent elongated pyloric segment. There is no indentation in the base of the cap.

*Case 2.** This patient was admitted to Tilton General Hospital on January 30, 1945, with an admission diagnosis of ulcer of the stomach. Digestive symptoms had their onset about February, 1943, while the patient was on duty in Iceland. The symptoms consisted of anorexia and vomiting about five minutes after meals, occasional lower abdominal cramps, burning sensation behind the sternum, and crampy midline abdominal pain appearing about one hour after meals and lasting from three to four hours.

On admission the patient appeared fairly well developed but somewhat below

* We are indebted to Dr. Jack Berk, who followed case 2 at Tilton General Hospital. A further report on this case is to be published by him.

optimal weight. There was tenderness in the midepigastrium. The liver could be felt one and a half fingerbreadths below the costal cage on deep inspiration. All other physical findings were negative. Laboratory studies were nonrevealing save for the presence of occult blood in the stools in grades ranging from a trace to 3 plus.

Roentgen-ray examinations were remarkable only for the demonstration of an elongation of the pylorus, which remained unchanged on recheck study 26 days later. Gastroscopy showed a superficial gastritis involving the fundus of the stomach. Gastric analysis disclosed a postprandial hyperacidity grade I and marked hypomotility.

On March 14, 1945, an exploratory laparotomy was done. A dense adhesion was noted extending from the liver edge to the lesser curvature of the stomach approximately one and a half inches proximal to the duodenopyloric junction. The pylorus and pyloric section of the stomach were normal to palpation. A longitudinal incision was made in the pyloric portion of the stomach. Examination of the biopsy sample disclosed a thickened layer of muscle and what was interpreted as chronic gastritis affecting the submucosa.

His postoperative course was uneventful except that abdominal symptoms continued just as prior to operation. Recheck gastric analysis disclosed no remarkable change from that before operation. Recheck gastrointestinal roentgen-ray series showed a slightly wider pyloric canal than previously but no other notable change. Another attempt at gastroscopy following operation was unsuccessful. The patient was discharged from the Army because of his inability to subsist on Army rations. His condition was considered as improved but not corrected.

I have followed this patient since 1946. His symptoms and roentgen-ray findings have remained unchanged throughout the last three years. He has refused further surgery, although he has moderate gastric stasis.

Discussion

The preceding cases reflect the difficulty in arriving at any certain diagnosis. In case 1, the presence of a high lesser curvature ulcer and an irregular thickening in the pyloric canal pointed to either a secondary benign ulcer in the pylorus, with secondary stenosis or spasm, or to an independent neoplasm in the pylorus. Gastroscopy was of little aid. The finding of the hypertrophic muscle on surgical resection and the additional gastric lesions were of no aid in establishing the etiologic sequence. It is possible that the muscle hypertrophy was secondary to the other gastric lesions. With repeated pylorospasm and continued stress, the pyloric muscle may have enlarged. It is a more tenable theory that the gastritis and ulcers were secondary to the varying degree of stenosis and stasis. I favor the latter concept because we have seen many cases of benign gastric ulcer in both the pyloric canal and elsewhere, and many cases of gastritis have been followed for several years without any hypertrophy of the pyloric muscle resulting.

In case 2, the study with all our armamentarium failed to exclude a pyloric neoplasm, and exploratory surgery had to be done.

Since there is no characteristic clinical or laboratory sign to point exclusively to this diagnosis, it becomes mandatory to explore all cases where these findings are present.

Conclusion

1. Hypertrophic pyloric stenosis in adults has assumed definite importance as a disease entity.

2. Clinically and roentgenologically there are no characteristic findings to differentiate it from other pyloric conditions.

3. Surgery is indicated in all cases presenting a persistent elongated pyloric canal.

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CO-EXISTING LOBAR ADENOCARCINOMA AND CYSTIC DISEASE OF THE LUNG*

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New York, N. Y.

The following case report deals with a patient with cystic disease of the lung who subsequently developed an unusual type of carcinoma in the same lung.

Case Report

A white male, aged 59, was admitted to the Jewish Memorial Hospital on February 18, 1947. He had been complaining of cough and expectoration of purulent sputum for 15 years. He had been hospitalized at various hospitals on a number of occasions as a suspected case of pulmonary tuberculosis. Roentgen-ray examination of the chest invariably showed multiple cystic areas in the right upper lung field with occasional fluid levels, while the left upper lung field had the appearance of bullous emphysema. Repeated sputum examinations were negative for tubercle bacilli. Between 1940 and 1942, he was followed at the N. Y. Health Department Chest Clinic. Roentgenogram of the chest on July 18, 1940 (figure 1) again revealed cystic areas in the right upper lung field with fluid levels; bullous emphysema was noted on the left side. Sputum examinations were persistently negative for tubercle bacilli. The findings were considered to be those of cystic lung disease.

In the spring of 1946, following a lapse in medical observation of several years,

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From the Department of Pulmonary Diseases, Jewish Memorial Hospital, New York, N. Y.

he began to complain of increasing dyspnea, weakness and severe cough. He was compelled to abandon his occupation as an elevator operator, and was finally admitted to the Jewish Memorial Hospital.

Physical examination revealed a severely dyspneic white male with marked cyanosis of the lips and fingers. The trachea was retracted to the right side. Examination of the lungs revealed dullness on the entire right side of the chest, with

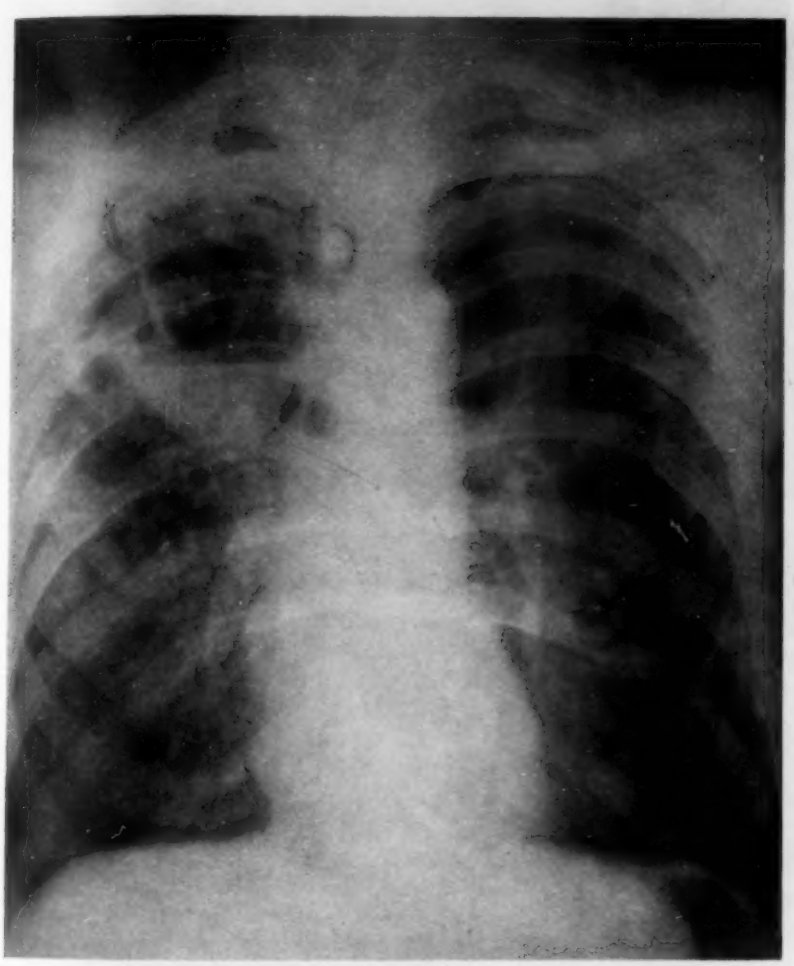

FIG. 1. Chest x-ray July 18, 1940. Multiple cystic areas in upper right lung field. Two fluid levels are visible. Bullous emphysema of upper left lung field.

flatness at the base. Bronchial breathing was audible over the anterior right chest, and whispered pectoriloquy was elicited. Crepitant râles were heard at the left base posteriorly. The heart sounds were of poor quality; no murmurs were heard. The apex beat was displaced to the right. Blood pressure was 130 mm. Hg systolic and 70 mm. diastolic. The liver was palpable one fingerbreadth below the right costal margin. There was no clubbing. No peripheral edema was noted. No glands were

palpable. The pulmonary findings were considered consistent with those of atelectasis of the right lung.

Roentgenogram of the chest on February 19, 1947 (figure 2) revealed a dense homogeneous opacity of the right hemithorax, with retraction of the mediastinum, trachea and heart to the right side. The left upper lung field had the appearance

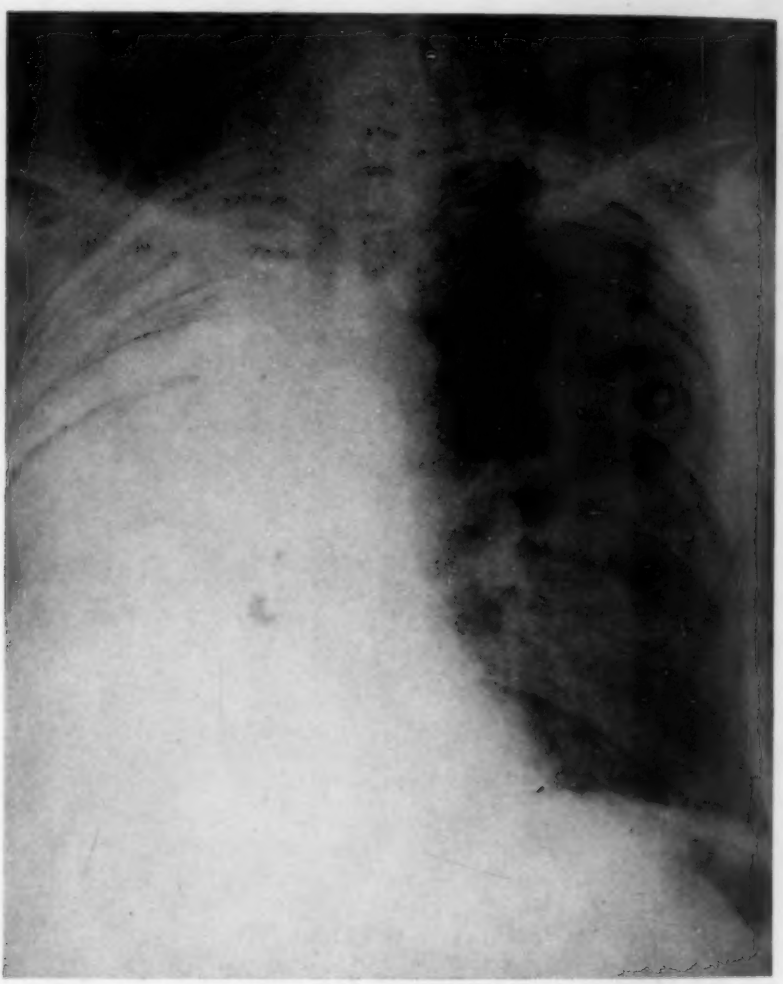

FIG. 2. Chest x-ray February 19, 1947. Homogeneous opacity of right hemithorax. Retraction of trachea and mediastinal structures to right side. Bullous emphysema of upper left lung field. Mottled infiltration in lower left lung field. Increased density at left base.

of bullous emphysema. A mottled infiltration was present in the lower third of the left lung field.

A diagnosis of endobronchial carcinoma of the right lung was made. Bronchoscopy on February 28 was negative for intrabronchial pathology. Bronchography revealed displacement of the trachea to the right side. The right main bronchus

and its main divisions were normally outlined. However, the remainder of the bronchial tree appeared contracted, with stunted small bronchi.

Aspiration of the chest yielded 420 c.c. of sanguineous fluid, which was replaced by 200 c.c. of air. Roentgenogram of the chest after this procedure showed a localized pneumothorax at the right base, with dense adhesions between the lung, the lateral thoracic wall and the diaphragm. The lung itself appeared solid and con-

FIG. 3. Right lung, showing abscess cavity (a) about 3.5 cm. in diameter around right main bronchus (b).

tracted. Histologic studies of the aspirated fluid failed to reveal any tumor cells. Sputum examinations were negative for tubercle bacilli. Repeated blood counts showed a moderate secondary anemia. The sedimentation rate ranged between 113 and 125 mm. (Westergren). The Wassermann test was negative. Blood chemistry studies were within normal limits. The temperature was elevated, at times reaching 102° F.

On March 17 the patient developed marked ankle edema, the neck veins became markedly distended, and the liver measured two fingerbreadths below the right costal margin. Dyspnea became increasingly severe and cyanosis more intense, the patient finally dying on March 18, 1947.

Postmortem Findings (limited to chest incision): The pleural cavities contained no excess of fluid. The entire right lung was massively adherent to the chest wall, with the parietal pleura presenting a thickness of about 1 cm. The lung could only be removed by sharp dissection. The entire right lung was quite solid and firm. When the bronchial tree was opened, the mucosa was found to be reddened and the lumen contained mucus. Around the right main bronchus there was an abscess about

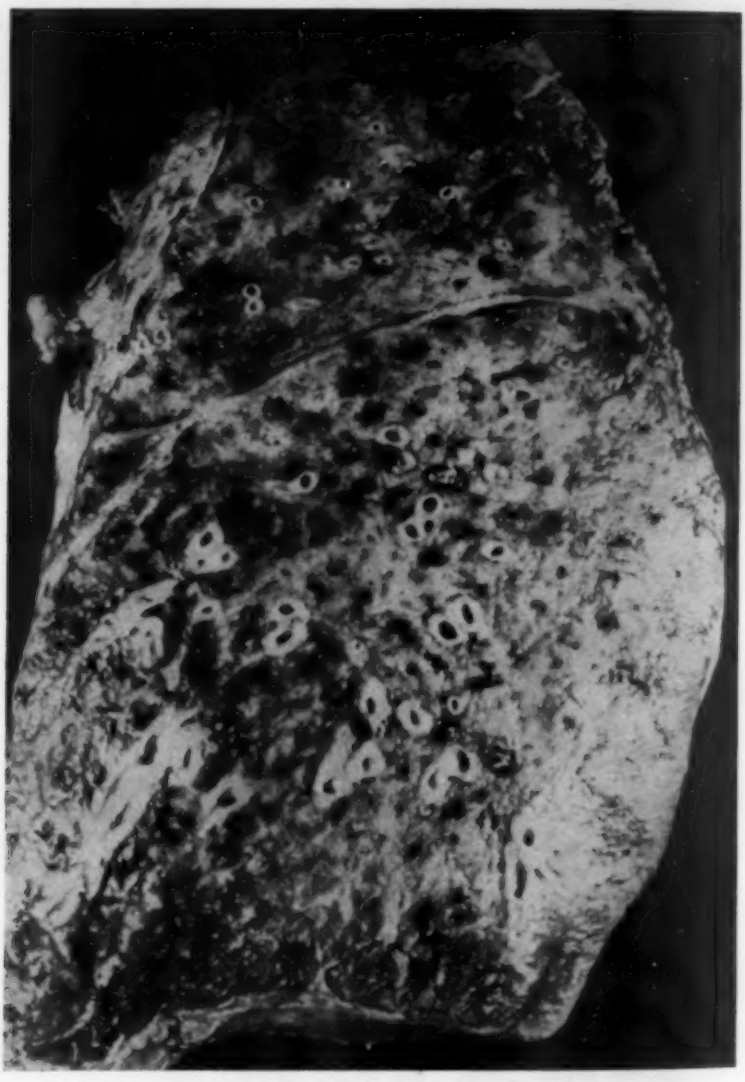

FIG. 4. Right lung, showing extensive consolidation.

3.5 cm. in diameter, containing frank yellow pus which was odorless (figure 3). Culture of this pus was sterile and no bacteria were seen. On careful dissection of the bronchi, no obstruction could be demonstrated, but dissection into the smaller bronchial branches was impossible because of the massive consolidation of the entire lung (figure 4). The right lung proper showed a whitish-gray appearance on section and cut like cartilage. Several small abscesses were found along the base of the lower lobe and also in the middle lobe. The apex showed some small calcified foci. The bronchial structures were encompassed by whitish firm tissue, and some scar tissue was also found in the upper lobe.

The left lung showed a quite different appearance. Some retracted scar tissue was found in the apex, and extensive bullous emphysema of both lobes of the left lung was present. There was no evidence of adhesions on this side. The mediastinal lymph nodes were markedly enlarged, and some of them were white and granular in appearance on section. A frozen section taken from these nodes showed definite invading atypical epithelial cells.

The heart was markedly enlarged, with considerable hypertrophy of the right side which measured about 2 cm. in thickness. The endocardium glistened. The valve structures were natural. The coronary arteries were patent throughout.

Inspection and palpation of the abdominal organs did not reveal any gross pathology.

Microscopic Findings: Heart showed areas of fibrosis and some fragmentation of muscle fibers.

Right lung showed diffuse infiltration by groups of atypical epithelial cells, some of them showing acinar arrangement (figure 5). The features of the individual cells, however, were those of squamous cells, with distinct cell membranes and areas of intercellular bridges. The tumor infiltrated the adjacent pleura and diaphragm. There were some areas of necrosis.

Bronchus showed the mucosa fairly intact, but the bronchial glands showed transformation of their ducts with anaplastic tumor tissue (figure 6).

Bronchial lymph nodes showed metastatic carcinoma.

Section from region of mediastinum showed an abscess adjacent to one of the main bronchi.

Liver showed massive fatty changes.

Anatomic Diagnoses: 1. Massive pneumonic carcinoma of the right lung with glandular and squamous cytological features. 2. Metastasis to mediastinal lymph nodes. 3. Abscess, massive, right lung. 4. Complete adhesion and thickening of parietal pleura. 5. Cor pulmonale. 6. Bullous emphysema of left lung, hilar.

Comment

At autopsy the patient presented a most interesting pneumonic carcinoma of the right lung, involving all but the upper lobe. This carcinoma showed glandular features throughout but with cytologic appearances suggesting squamous features as well. The impression was that the tumor had taken its origin from the duct structures of the glands of the bronchus. In addition, the right upper lobe showed a large abscess cavity containing sterile pus. The findings suggested that cystic disease with emphysema and secondary abscess formation preceded the development of carcinoma, which was of more recent occurrence. The patient showed a cor pulmonale and considerable emphysema. The absence of any bronchoscopic findings was compatible with the lack of bronchial involvement in the gross examination.

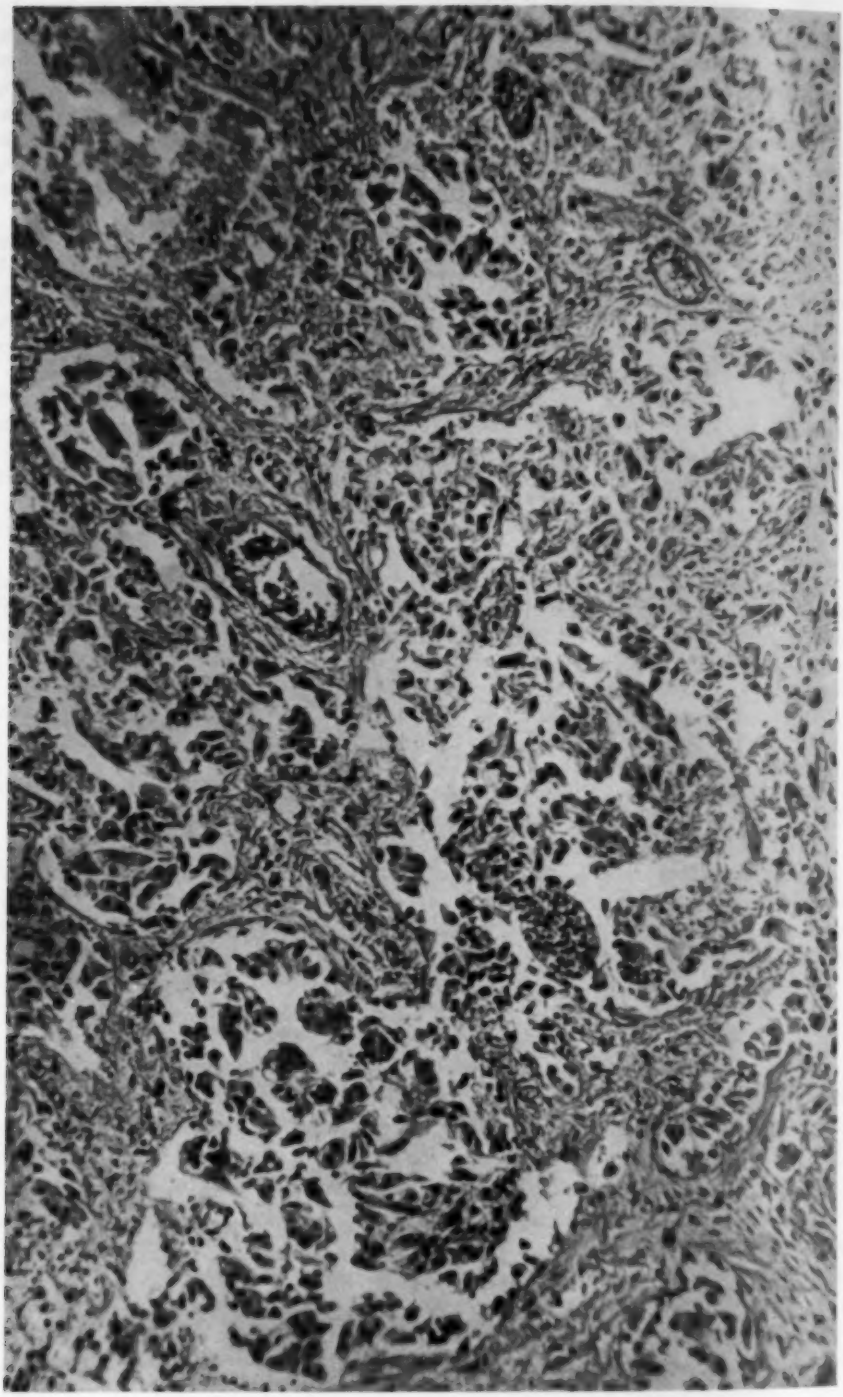

FIG. 5. Section of right lung, showing carcinoma cells lining alveolar spaces.

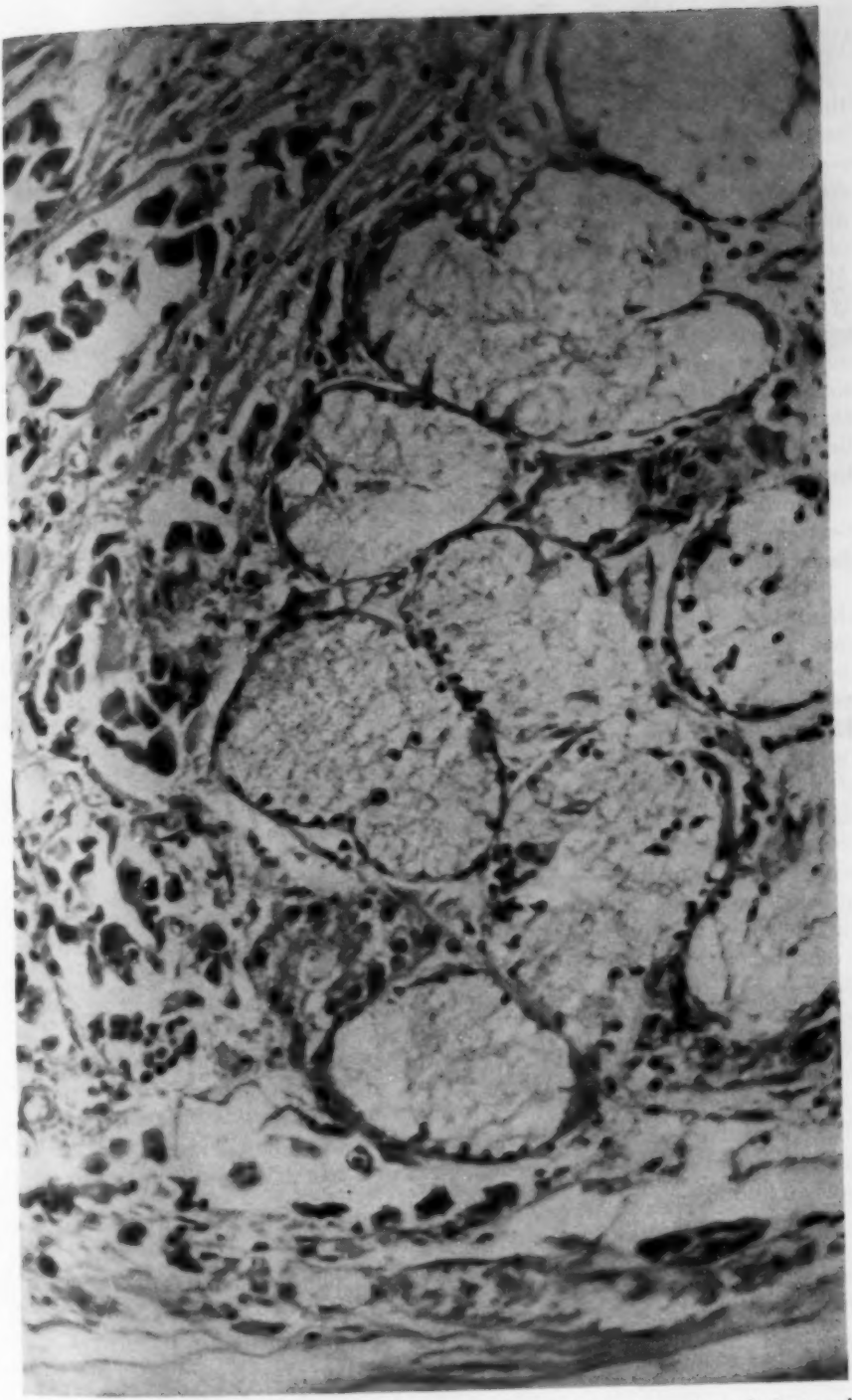

FIG. 6. Section of right lung, showing bronchial glands. Transformation of ducts with anaplastic tumor cells.

Discussion

A review of the literature indicates that the coexistence of carcinoma and cystic disease of the lung has not received much attention. It is possible that this may be due to the difficulty encountered in distinguishing between cavitating carcinoma and a pulmonary cyst with subsequent carcinomatous change.

Womack and Graham [1] reported epithelial hyperplasia and metaplasia in congenital cystic disease of the lung and discussed its possible relation to carcinoma of the bronchus. Of nine cases in whom surgical removal of a part or of an entire lung was done, three cases showed evidence of metaplastic change. Moersch and Clagett [2] reported 44 cases of pulmonary cysts of bronchiogenic type. They felt that bronchiogenic cysts are lined by a type of mucosa that might lend itself to the development of carcinoma. In their study two cases were encountered which, from the duration of symptoms, the findings at the time of operation, and microscopic examination of the tissue, seemed to indicate that carcinoma had developed secondarily in a pulmonary cyst. Graham [3] believes that there is a great tendency for cystic disease of the lung to develop into carcinoma.

Korol [4] followed 40 cases of congenital cystic emphysema of the lung for 15 years and noted that seven of these cases died of bronchial carcinoma, an incidence of 18 per cent.

The patient reported in this paper had been under medical observation for about 15 years for his chest complaints. The earliest roentgenogram which could be obtained indicated that in 1939, eight years before death, he had cystic disease of the lungs. For a period of four years (1939–1942), during which he had frequent chest roentgenograms, the findings in the lungs were those of cystic disease with emphysema. Fluid levels of varying degree were demonstrated in the right lung.

The type of carcinoma found at post mortem was unusual in that it had the characteristics of an extensive pneumonic consolidation and microscopic study revealed diffuse adenocarcinoma. As pointed out by Silverman and Angrist,[5] such tumors, although included in all anatomic classifications of pulmonary tumors, are distinctly infrequent. No primary adenocarcinoma can be found outside the lungs, nor can an exact origin from a bronchus be demonstrated. According to Silverman and Angrist, they presumably arise from the mucosa of the bronchial tree beyond the larger bronchi, the point of origin being obscured by the extensive growth involvement. These same authors do not find any relationship between diffuse adenocarcinoma of the lung and pulmonary adenomatosis.

As far as can be determined, it would appear in this case that the cystic disease antedated the development of carcinoma. The coexistence in the same lung of lobar adenocarcinoma and cystic disease is believed to represent an unusual finding.

Conclusions

1. A case of lobar adenocarcinoma of the lung occurring in a patient with cystic lung disease is reported.

2. Attention has been drawn to the possible relationship between cystic disease of the lung and carcinoma of the lung.

The authors wish to express their gratitude to Dr. Alfred Angrist and to Dr. Alfred Schwarz, of the Department of Laboratories, Jewish Memorial Hospital, for their assistance in the preparation of the pathologic section of this paper, and to Dr. Milton A. Miller for permission to publish this case.

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DISSECTING ANEURYSM OF THE AORTA WITH PERIPHERAL EMBOLIZATION: A CASE REPORT *

By William C. Schraft, Jr., M.D., *New Rochelle, N. Y.*, and James R. Lisa, M.D., F.A.C.P., *New York, N. Y.*

Dissecting aneurysm of the aorta is a fairly common finding at the autopsy table. Its incidence has been reported as approximately one in 400 necropsies. At City Hospital there have been 16 cases autopsied in the past 22 years, a ratio of approximately one in 355 necropsies. Nearly 800 cases have been described in the literature. So far as could be determined, multiple distant embolizations due to mural thrombi located at the site of intimal rupture have not previously been observed. This communication is the report of such a case.

Case Report

The patient was a white woman, 64 years of age, who had never previously been ill. She was first seen by a physician on June 30, 1948, in profound shock, the pulse rapid and thready, the blood pressure unobtainable, and the heart sounds muffled. A few hours previously she had complained of mild precordial pain. Hospitalization was refused. On the following day she not only appeared perfectly well when seen by her physician but had actually done some shopping. Four days later the picture of profound shock again appeared, at this time associated with cramp-like, nonradiating precordial pain. Gross hematuria developed three days later. She again apparently recovered. Ten days later, while walking about the house, she noticed sudden sharp pain in the right lower extremity which radiated from the hip to the toes. The pain increased in severity and 24 hours later she was removed to the hospital.

At time of admission the pain in the extremity seemed less severe and was described as cramp-like in character. The right lower leg was cold, the lower third cyanotic; the toes were white and the foot was completely anesthetic. Femoral, popliteal and dorsalis pedis pulsations were unobtainable. The patient, however,

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From the Division of Pathology, City Hospital, Welfare Island, Department of Hospitals, New York, N. Y.

lay quietly in bed and did not appear in acute distress. Further physical examination revealed nothing of note. Temperature was 101° F., pulse was 90, respirations were 22, and blood pressure was 118 mm. Hg systolic and 80 mm. diastolic. Electrocardiographic tracings on two occasions were interpreted as showing mild disease of the ventricular musculature without acute change. Roentgenology showed the cardiac shadow to be enlarged to both sides; the aortic bend was widened, and the aortic knob was accentuated. Blood chemical tests, urinalyses, blood culture, bleeding and

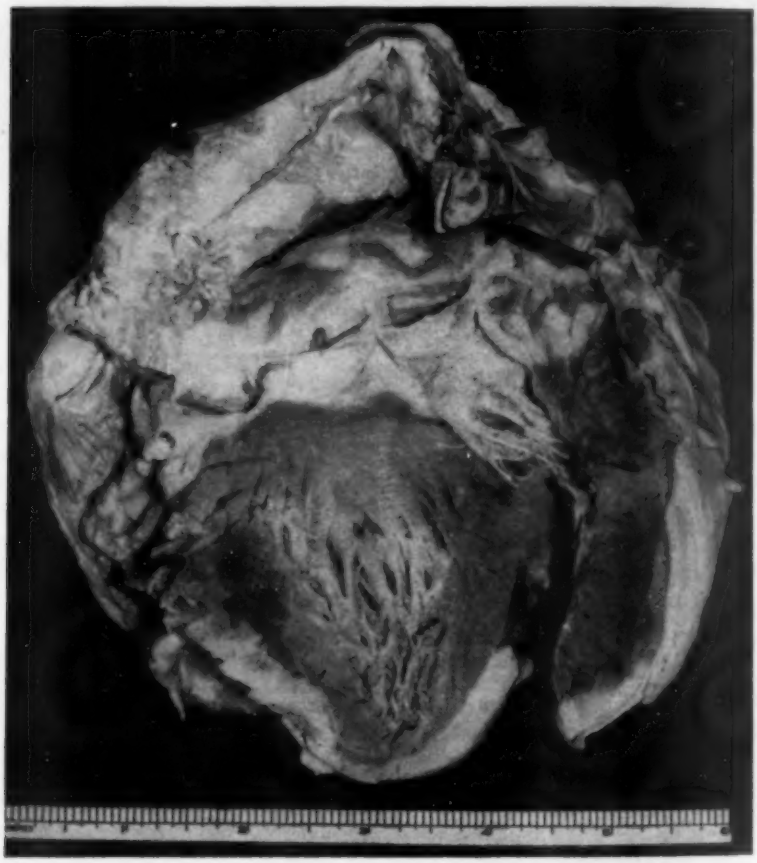

FIG. 1. Heart and aorta showing the transverse intimal tear and a friable mural thrombus (arrow). A second thrombus (not shown in photograph) was detached during fixation.

clotting time, and prothrombin time were normal; sedimentation rate was greatly increased.

On the second day, absence of the right radial pulse was noted; the axillary pulse was normal. A stellate ganglion block was performed with satisfactory results; a Horner's syndrome developed, and the right hand became warmer.

On admission, anticoagulant therapy was begun. Heparin was given for 30 hours, followed by Dicumarol, which was continued throughout the course, the prothrombin time being maintained between 25 and 38 per cent of normal. Lumbar

paravertebral blocks were carried out daily for the first five days. In spite of these measures, the condition of the right leg became progressively worse and supracondylar amputation, performed under ice anesthesia, became necessary on the tenth day. Two days later the patient developed a right hemiplegia with right facial paresis. Death occurred 48 hours later.

The clinical diagnosis was acute myocardial infarction with mural thrombosis and peripheral embolization.

Pathological Report: The specimen consisted of a right leg, amputated above the condyle, showing greenish-black discoloration of the entire foot and distal third of the leg. The popliteal artery was completely occluded by a gray embolus located 2 cm. below the point of amputation and extending peripherally to the bifurcation of the artery. The popliteal vein was normal. Histologically, the wall of the popliteal artery was normal. An organized embolus, well attached to the intima by proliferating fibroblasts, was present.

Necropsy Report: Performed 18 hours after death. Only the pertinent data are abstracted. The heart was grossly normal. In the ascending aorta, 3 cm. above the valve, a transverse intimal tear 6 cm. in length was noted, this being the point of intimal penetration for a dissecting aneurysm (figure 1). The dissection progressed cephalad for 2 cm. and continued proximally for several centimeters where, at an unknown point, it ruptured into the pericardial sac. The sac contained 300 c.c. of clotted blood. Along the line of intimal tear there were three friable thrombi, the largest measuring 2 cm. in greatest diameter.

Histologically, the ascending aorta showed moderate atherosclerosis, with the deposition of cholesterol crystals within the intima. In the middle third of the media there was a cystic area of degeneration containing a mucoid-like material; there was no adjacent cellular response. The vasa vasorum were normal. Sections through the aneurysm showed the dissection to have occurred along the inner third of the media, the area being filled with clotted blood.

The right femoral artery was completely occluded by an embolus, purplish in color, extending from 3 cm. distal to Poupart's ligament to the amputation site. Histologically, the vessel wall appeared normal; the embolus was attached to intima by a few fibroblasts. Similar emboli were found occluding the splenic artery and the left popliteal artery. Emboli of various ages were found in the smaller radicles of the renal arteries. Infarction of spleen and kidneys was noted. Permission to examine the brain was not obtained.

Comment

Dissecting aneurysm of the aorta has been attributed to cystic degeneration of the media followed by rupture, first through the inner layer, and frequently also through the outer zone, leading to massive hemorrhage. First described by Erdheim [1] in 1925 under the term "medionecrosis aortae idiopathica," this lesion of the media has been found in the majority of the more recently reported cases. Obliterative endarteritis of the vasa vasorum, once advanced as the cause of the medial necrosis, has not been confirmed by later observations. The etiology is still obscure, although the toxic effects of active infection has been advanced as a possible cause. Death is due, in 95 per cent of the recorded cases,[2] to secondary complete rupture of the aortic wall and massive hemorrhage. In 70 per cent the rupture occurred into the pericardial sac, in 20 per cent into the left pleural cavity, and in 5 per cent into the mediastinum. Occasionally spontaneous healing occurs. Two such examples were present among the 16 cases on record at City Hospital. One had a healed transverse scar of the intima. The other had a

large diamond-shaped cavity communicating with the aortic lumen, completely covered by endothelium, the outer wall consisting of the outer half of the media and the adventitia.

The formation of mural thrombi at the intimal lesion with peripheral embolization appears quite physiologic. The rarity of its occurrence is unexplainable.

Conclusion

A case of dissecting aneurysm of the aorta with mural thrombosis and peripheral embolization is reported. Review of the literature failed to reveal the report of a similar case.

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PENICILLIN–CARONAMIDE THERAPY OF ENTEROCOCCUS ENDOCARDITIS *

By Russell P. Hager, Ph.D., M.D., Edward J. Heitzman, M.D., and Raymond M. Young, Ph.D., *Providence, Rhode Island*

Enterococcus endocarditis has been shown to be particularly resistant to treatment. Of the unsuccessfully treated cases of bacterial endocarditis, the most frequent resistant organisms have been noted to be enterococci.[1] Clark, Bryner and Rantz [2] have stated that enterococci always tolerate higher penicillin concentrations than other streptococci, and although most species of streptococci occurring in this type infection are inhibited by 0.1 unit of penicillin per ml. of culture medium, the enterococci require over 0.5 unit and occasionally up to 50 to 100 units, the majority being inhibited by between 5 and 10 units. In order to attain therapeutic blood concentrations, 10 to 20 million units of penicillin per day may be required. It has become apparent that many of the earlier failures in the management of endocarditis due to enterococci were the result of inadequate dosage.

To achieve high concentrations of penicillin in the plasma, it is necessary to administer massive doses of the antibiotic, to block its excretion, or both. Bryner and his co-workers [3] demonstrated that a rate of intravenous injection of 3 million units per hour is required to exceed the excretory capacity of the renal tubules. Administration of 10 to 20 million units per day at a rate of 500,000 units intravenously per hour produces the serum concentrations of 6 to 20 units per ml. necessary to inhibit most enterococci.

A number of methods for delaying excretion of penicillin have been reported, including the use of diodrast,[4] para-amino hippuric acid,[5] benzoic acid with salt

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From the Medical Service, Rhode Island Hospital, Providence, Rhode Island.

and water restriction [6] and caronamide.[7] Because of its low toxicity and ease of administration, caronamide appears to be the most practical for clinical use.[8, 9, 10, 11] Concentrations as high as 300 units per ml. have been attained by the combined use of caronamide and massive doses of penicillin.[11, 12] By tubular blocking and appropriate penicillin dosage, inhibitory concentrations in vivo usually can be obtained. Occasionally a very resistant strain of enterococcus may be encountered which will not yield to combined penicillin-caronamide therapy; therefore, it is important to know the penicillin sensitivity titer of the organism.

The following case report demonstrates the use of penicillin and caronamide in the successful treatment of subacute bacterial endocarditis caused by a member of the enterococcus group of streptococci.

Case Report

This was the second Rhode Island Hospital admission of a 34 year old white married female who entered because of chills, fever and malaise of seven weeks' duration.

Past History: The patient denied serious childhood diseases, including scarlet fever. At the age of 12 years the patient had episodes of epistaxis; no history of arthritis or myalgia was obtained. When she was 27 years old she experienced transient ankle edema, followed by increasing exertional dyspnea and attacks of paroxysmal nocturnal dyspnea. Two years later she entered the Rhode Island Hospital for the first time because of periorbital and dependent edema. Physical examination revealed a blood pressure of 160 mm. Hg systolic and 90 mm. diastolic, 3 plus pitting edema of the ankles, a heart enlarged in its transverse diameter, with systolic and diastolic murmurs at the apex, and congestive changes in the lungs. After 13 days of bed rest in the hospital, she was discharged with a diagnosis of inactive rheumatic heart disease with mitral stenosis and insufficiency. After several weeks of bed rest at home, she recovered and carried on without medication, her activity being limited only by exertional dyspnea.

Present Illness: Several weeks before this admission she had a tooth extracted; two days later she began to have generalized weakness, easy fatigability and chilly sensations. One week later, spontaneous abortion of her two-month pregnancy occurred. Since that time her symptoms had become progressively more severe and she was confined to bed. She experienced anorexia, fever of 104° F., shaking chills and persistent vaginal bleeding. She received no specific medication but was referred to the hospital with a diagnosis of bacterial endocarditis.

On admission, physical examination revealed a temperature of 102.2° (rectal), pulse 94, respirations 40, and blood pressure 115 mm. Hg systolic and 50 mm. diastolic. She was a well-nourished, well-developed white woman with a pallor described as café-au-lait. Careful search, including conjunctivae and fundi, revealed no petechiae. The mucous membranes were pale, the neck supple, the trachea in the mid-line, the thyroid not enlarged, and the lungs clear. Examination of the heart revealed a diastolic thrill at the apex and enlargement by percussion to the left anterior axillary line in the fifth interspace. There was a harsh systolic murmur over the entire precordium, with maximum intensity at the apex. A rumbling diastolic murmur with a presystolic crescendo was audible near the apex. The rhythm was regular, P_2 louder than A_2. A smooth, non-tender liver edge could be palpated one finger-breadth below the right costal margin, and the tip of the spleen was felt on inspiration. No other organs or masses were felt. Pelvic examination revealed dark brown hemolyzed blood in the vagina and moderate tenderness of the body of the uterus and the left uterosacral ligament. The extremities showed early clubbing of

the fingers but no edema, tenderness or cyanosis. Dorsalis pedis pulsations were strong and equal. Deep reflexes were physiologic.

Initial Laboratory Work: Sedimentation rate 60; Hinton, negative; blood urea nitrogen 11; blood glucose 116; red blood cells 3,310,000; hemoglobin 7.7 gm./100 ml.; white blood cells 6,300 with neutrophils 81 per cent, lymphocytes 11 per cent, monocytes 8 per cent. Urinalysis: color, amber; specific gravity 1.014; pH 6; protein 0; sugar 0; sediment heavy with 1 red blood cell, 4 white blood cells, and a few fine granular casts per high power field. A nose and throat culture was negative for hemolytic streptococci.

Chest Roentgen-Ray: Heart shadow was markedly enlarged, transverse diameter 15.2 cm. as compared with a transverse chest diameter of 23.5 cm. Left cardiac border showed prominent bulging in the region of the left auricle, a contour characteristic of rheumatic heart disease. The lower two-thirds of both lung fields showed moderate hazy density, with fine-to-coarse mottling due to moderate vascular congestion. Both diaphragms normal. No effusion. Visible bony parts disclosed no abnormalities.

Course: On admission the patient was placed at bed rest. A blood culture was drawn. Another blood culture was taken on the following day. During her second night in the hospital she complained of headache, became lethargic, voided incontinently, and was unable to move her left arm and leg. In the morning there was nuchal rigidity with weakness of the left face and flaccid paralysis of the left arm and leg. Deep reflexes were hyperactive. A positive Babinski sign and ankle clonus were elicited on the left. At this time, the laboratory reported growth of a hemolytic enterococcus (*Streptococcus zymogenes*), 33 colonies per ml. of blood. Penicillin therapy was instituted with 200,000 units intramuscularly every three hours. On the next day, sensitivity tests revealed that 1.95 units of penicillin per ml. but not 0.97 unit per ml. inhibited growth of the organism. Therefore, on the fourth hospital day the dosage of penicillin was increased to 400,000 units every three hours intramuscularly. Her temperature, however, remained elevated above 100° rectally, and five days later blood penicillin assays were performed (see table 1). With this dosage, a therapeutic concentration was maintained for only one hour; accordingly, caronamide (Staticin) was administered by mouth, 3 gm. every three hours. Following the first dose there was little effect on the blood penicillin concentration, but after 24 hours of this combined penicillin-caronamide therapy, adequate concentrations were observed for the entire interval between injections. Nevertheless, in order to raise the blood concentration to at least four to five times that found necessary to inhibit this strain of enterococcus in vitro, the dosage of penicillin was increased to 600,000 units every three hours. This course of therapy was maintained for 29 days. Weekly blood assays were obtained showing a range of 3.8 to 15.4 units per ml. Blood cultures with penicillinase added to the medium were consistently sterile.

The patient's clinical course was very satisfactory. Following the fifteenth hospital day her temperature, pulse and respirations remained at normal values. Her headache and stiff neck gradually subsided and the sensorium cleared. There was progressive return of neuromuscular function of the affected left side. With massage and active and passive exercise she regained almost normal use of her arm and leg. The liver and spleen receded above the costal margins. On admission, the electrocardiogram showed notching of the P waves in Lead I, with low voltage of the QRS complex in the standard leads. Subsequent tracings showed a pronounced increase in voltage of the QRS complex; the P waves became relatively large and notched or diphasic in various leads.

Following administration of caronamide, the urine and peripheral blood were examined daily. Urinary tests for protein became positive and increased to 3 plus.

Although the blood glucose was normal, a reducing substance appeared in the urine, giving reports of trace to 2 plus sugar. Acetone tests were consistently negative. Caronamide crystals appeared in the urine. There were variable numbers of white blood cells and red blood cells. When caronamide was discontinued, tests for protein showed only a trace; those for sugar were negative. At no time was there evidence of suppression of hematopoiesis. During caronamide therapy, the following blood chemistry values were obtained: urea nitrogen 10; glucose 84; protein 6.6; and NaCl 4.63 mg. per cent. At the time of discharge, the values were urea nitrogen 7; blood glucose 81; red blood cells 4,340,000; hemoglobin 11.8; white blood cells 8,500, with 69 per cent neutrophils, 22 per cent lymphocytes, 7 per cent monocytes, and 2 per cent eosinophils.

The patient had continued to bleed vaginally and so, 17 days after omission of penicillin and caronamide for the bacteremia, she received prophylactic doses of penicillin, and on the following day a dilatation and curettage was performed. Curettings were identified as degenerated placental tissue with post-abortal endometritis. She remained afebrile and two days later left the hospital, asymptomatic except for left facial and left arm weakness. Since then weekly blood cultures have been sterile. Three weeks after discharge, pelvic examination in the Gynecological Follow-up Clinic was normal. Uncorrected Wintrobe sedimentation rates of 34, 33 and 38 mm. per hour were observed during the month following discharge. Two months after discharge, the sedimentation rate was 21 mm. per hour; four months after, it was 17 mm. per hour.

Methods: The procedure followed in the identification of the etiologic bacterial species was that used routinely for identifying streptococci in the enterococcus group. The organism fermented mannitol and was able to grow in 40 per cent ox-bile broth, 5 per cent NaCl broth, and at 45°C. The enterococcus was identified as *Streptococcus zymogenes* because it fermented sucrose, reduced litmus milk rapidly, and produced clear zone hemolysis on blood agar. The technic employed in the sensitivity titer determinations was a modification of the Rammelkamp-Keefer serial dilution method.[13] Blood serum penicillin determination was carried out by means of the serial dilution technic, in which the standardized test species was a strain of *Streptococcus viridans* which was inhibited by 0.008 unit of penicillin per ml., but not by 0.004 unit per ml.

Discussion

The present case demonstrates the importance of accurate identification of the pathogenic organism and determination of antibiotic sensitivity. The finding of a member of the enterococcus group invariably indicates an organism considerably more resistant to penicillin than other species of Streptococcus; consequently, a more rigorous therapeutic routine must be followed. The etiologic agent in the above case was identified as *Streptococcus zymogenes,* which is a hemolytic streptococcus, a member of the enterococcus group occurring in Lancefield's Group D classification of beta streptococci. This species was originally isolated from a case of acute endocarditis.[14]

Since between one and two units of penicillin per ml. were required to inhibit the etiologic agent in vitro, the organism would be considered moderately resistant from the therapeutic standpoint without use of caronamide. Using penicillin alone, massive doses would have been required to cope with the infection; however, by administering caronamide with the antibiotic, it was possible to ob-

tain satisfactory blood concentrations with reasonable quantities of penicillin. As indicated in the table, two hours after administration of 400,000 units of penicillin intramuscularly, 0.7 unit per ml. was detected in the blood serum; three hours after injection, only 0.2 unit remained. However, after 24 hours of caronamide therapy and the same periodic dose of penicillin, 3.8 units per ml. were present three hours after the preceding penicillin dose. This represents an increase of over 19 times the previous concentration. This treatment schedule maintained a therapeutic level at all times. Others [2] have recommended that, in the treatment of subacute bacterial endocarditis, the penicillin concentration in vivo should be four to five times that necessary to inhibit the organism in vitro.

TABLE I

Blood Penicillin after Intramuscular Penicillin and Oral Caronamide (Staticin)

Date	Penicillin Dosage Every 3 Hours	Caronamide Dosage Every 3 Hours	Time Interval after Given Dose	Units Penicillin per ml. Serum
7- 9-48	400,000	none	1 hr.	2.9
			2 hr.	0.7
			3 hr.	0.2
7- 9-48	400,000	3 gm. (1st dose)	1 hr.	1.4
			2 hr.	1.4
			3 hr.	0.7
7- 9-48	400,000	3 gm. (7th dose)	1 hr.	5.8
			2 hr.	5.8
			3 hr.	3.8
7-16-48	600,000	3 gm.	1 hr.	7.7
			2 hr.	7.7
			3 hr.	3.8
7-23-48	600,000	3 gm.	1 hr.	15.4
			2 hr.	7.7
			3 hr.	3.8
7-30-48	600,000	3 gm.	1 hr.	11.5
			2 hr.	11.5
			3 hr.	5.8
8- 7-48	600,000	3 gm.	1 hr.	11.5
			2 hr.	7.7
			3 hr.	3.8

Therefore, 600,000 units of penicillin were administered every three hours with caronamide. The higher dosage resulted in consistently higher blood penicillin values, as shown in table 1.

Because of the normal blood glucose and the appearance of a reducing substance in the urine, various tests were performed to identify the substance. Benedict's test was positive, hot but not cold; Nylander's reaction, trace; Enklewitz' test and Bial's test were negative for pentose. The reducing substance was removed by treatment with charcoal (Norit). This is evidence in favor of a glucuronate rather than a pentose, as suggested by others.[15]

Caronamide was administered in therapeutic doses for 33 days without evidence of toxicity. Blood chemistry values remained normal, and there was no evidence of suppression of bone marrow. In this case there were no subjective symptoms such as nausea or vomiting. False-positive tests for proteins and glucose in the urine have been described.[15, 16] Our observations confirmed these findings, although the reducing substance in the urine was not a pentose but probably a glucuronate.

Conclusion

A case of enterococcus subacute endocarditis was successfully treated with penicillin and caronamide. High concentrations of penicillin were maintained in the blood for 29 days. Caronamide was administered for 33 days without evidence of toxicity, although a reducing substance, probably a glucuronate, appeared in the urine.

Note: As of December 29, 1950 the patient had remained well with no recurrence of the infection.

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EDITORIAL

RABIES: SOME CURRENT PROBLEMS AND RECENT IMPROVEMENTS IN MEASURES FOR ITS CONTROL

ALTHOUGH the epidemiology of rabies has been intensively studied and the measures necessary for its control have been reasonably well understood for many years, the disease continues to be a major problem from the standpoint of public health. During the past 16 years there has, in fact, been an increase in its occurrence in animals in many parts of this country which has been described as alarming.[1] The number of reported cases of the disease in man has not changed materially, ranging usually from 30 to 50 a year.[2] This low incidence, however, may be attributable, in part at least, to the vaccination of about 30,000 exposed persons annually, a tedious and painful procedure which is not without risk and which involves an estimated cost of five million dollars.

The number of cases reported in animals tends to show cyclical variations, and there was an upswing in the middle of the last decade. During 1940 to 1944 (inclusive) a total of 42,510 cases were reported. The bulk of these (36,756) were dogs, the remainder being chiefly cats and the usual domesticated farm animals, particularly cattle (1842 cases). There were also 1270 cases in other species of which the fox is by far the most important in the eastern United States.

Epizootics in foxes have been recognized since 1812 (in Massachusetts), and they have been particularly frequent and widespread in the southeastern states since 1938.[3] Widely distributed sporadic cases also occur. An extensive epizootic in foxes appeared in New York in 1945 along with canine rabies.[4] The total number of cases of rabies reported in New York increased from 64 in 1942 to 1174 in 1946. Of the latter, 377 were dogs, 308 foxes and 440 cattle, and in the first nine months of 1947 there were 40 dogs, 218 foxes and 173 cattle. The high incidence in cattle is attributed to fox bites inflicted in pastures.

Control of rabies in foxes presents manifest difficulties from the practical standpoint. It is equally obvious that rabid foxes constitute a serious danger, not only to cattle but to dogs and indirectly to man, as long as there is a susceptible canine population in the locality. Experience has shown that such epizootics tend to occur during cyclical increases in the fox population. As the latter falls as a result of deaths from rabies and other natural

[1] Steele, J. H., and Tierkel, E. S.: Rabies problems and control. A nation-wide problem, Pub. Health Rep. **64**: 785–796, 1949.

[2] Control of rabies. Report by the Committee on Public Health Relations of the New York Academy of Medicine, Pub. Health Rep. **62**: 1215–1237, 1947.

[3] Rabies and its control. Report of Subcommittee of Committee on Animal Health, National Research Council, J. Am. Vet. M. A. **108**: 293, 1946.

[4] Korns, R. F., and Zeissig, A.: Dog, fox and cattle rabies in New York State, Am. J. Pub. Health **38**: 50–65, 1948.

causes and the more susceptible animals are eliminated, the epizootic tends to die out spontaneously. This may be hastened to some extent by intensive trapping and shooting. The most effective feasible measure for protection from such epizootics, however, seems to be the annual vaccination of all dogs, which would tend to prevent both transfer of the infection to man and its subsequent re-introduction into a new susceptible fox population.

In other sections of the country different forms of wild life may be involved—coyotes in the western states and occasionally skunks.

In tropical South America and western Mexico a great many cases of rabies of the paralytic type have occurred, particularly in cattle, which were infected by bites of vampire bats. This form of rabies was first recognized in southern Brazil in 1911, bats being incriminated on epidemiological grounds. Rehaag later (1916) demonstrated rabies virus in these bats by inoculation of rabbits. The disease apparently spread southward into Argentina and northward to Venezuela, reaching the island of Trinidad in 1925. In 1929 and 1930, 17 persons in Trinidad died of an acute ascending myelitis which was regarded clinically as poliomyelitis. Rabies virus was eventually isolated from the brain of one of these cases, and subsequently by Pawan [5] from the salivary glands of the vampire bats. These bats usually die of the infection eventually, but some may live at least two to five months while harboring virus in the saliva and functioning as symptomless carriers of the infection. Pawan demonstrated Negri bodies in the brain of 3.8 per cent of 2292 bats, chiefly vampires, which were captured in Trinidad.

Verteuil and Urich collected 55 human cases of paralytic rabies in Trinidad, and obtained a history of a bat bite in all but one of 40 cases which they were able to study adequately. Curiously no human case of rabies of this type has been reported from continental South America or Mexico. Whether this is due to different environmental conditions or to inadequate diagnosis is uncertain, but the possibility of its transmission to man has been amply demonstrated.

The disease as it occurs in cattle in Mexico—derriengue—has recently been studied by Johnson.[6] It seems to have been present here for many years, and it is spreading inland from the Pacific coast. The losses have been severe—up to 10,000 cattle annually, and from 20 to 50 per cent of the cattle in an involved area during some epizootics.

Rabies in dogs, however, constitutes the major problem. That the control measures available are effective if adequately enforced is indicated by the experience of Great Britain, from which the disease has been eliminated. The success in preventing the re-introduction of rabies may be attributed in part to the absence of land boundaries but also to the rigorous quarantine for six months of all imported dogs. The need for such a protracted period

[5] Pawan, J. L.: Transmission of paralytic rabies in Trinidad by vampire bats (*Desmodus rotundus murinus* Wagner 1840), Ann. Trop. Med. **30**: 101–130, 1936.

[6] Johnson, H. N.: Derriengue: Vampire bat rabies in Mexico, Am. J. Hyg. **47**: 189–204, 1948.

is indicated by the fact that of 16 cases of rabies developing during quarantine, in four it appeared after more than four months and in one after more than six months.

The problem in this country is undoubtedly more complicated. Difficulties have been due in part to the diversity of control measures in different states and to the even greater differences in the rigor with which they are enforced. Uniform and adequate measures are essential for success, and these can be obtained practically only under the guidance and authority of a central agency. It is becoming increasingly clear, now that potent vaccines are available, that the usual measures should be supplemented by the universal vaccination of dogs.[2]

Several observers have reported differences in the virulence of various strains of street virus as determined by the duration of the incubation period in rabbits as well as by the titer of the infecting dose. Both attenuated strains and those of exceptionally high virulence ("reinforced") have been described in this country as well as in Europe. In certain instances virulent strains have been associated with human rabies with a short incubation period but by no means regularly, and further study is required to determine their significance.

Recent work on rabies vaccine has had two primary aims in view: first, the preparation of a uniformly potent vaccine which is "safe," and second, elimination of the severe reactions (paralytic accidents) which occur in a small but hitherto irreducible fraction of the patients treated.

A major step toward the first goal was the development of a reliable test by Webster,[7] later perfected by Habel,[8] using mice for measuring precisely the potency (immunizing power) of a vaccine. This test has since been adopted by the National Institute of Health for routine testing of vaccines before release for general use. A satisfactory vaccine must protect mice from at least 1000 LD_{50} under the conditions of the test, and the best preparations may protect from 50,000 doses.

Using this test, it was found that there were marked differences between various preparations of vaccine. In general those preparations containing attenuated but living virus gave more protection than those in which the virus was entirely inactivated. (This difference is not evident in the available statistics concerning their use in the vaccination of human subjects.[9]) The street virus (from dogs) undergoes marked alterations, presumably a mutation, in its conversion to fixed virus during repeated passages through rabbits by intracerebral inoculation, and nearly always, at least, it loses its capacity to infect animals when inoculated peripherally. There

[7] Webster, L. T.: A mouse test for measuring the immunizing potency of antirabies vaccine, J. Exper. Med. **70**: 87–106, 1939.

[8] Habel, K.: Evaluation of a mouse test for the standardization of the immunizing power of antirabies vaccine, Pub. Health Rep. **55**: 1473–1487, 1940.

[9] McKendrick, A. G.: Statistics on rabies. A ninth analytical review of reports from Pasteur Institutes on the results of anti-rabies treatment, Bull. Health Organ., League of Nations **9**: 31–78, 1940–1941.

has been a strong suspicion, however, that this loss may not invariably be absolutely complete. The incidence of paralytic accidents also seems to be about three times as great after attenuated vaccines as after inactivated ones.[8] In many Institutes, therefore, attenuated vaccines, such as the original Pasteur vaccine, have been replaced by phenolized (inactivated) vaccine of the Fermi or Semple type.

Examination of commercial preparations of the Semple vaccine a decade ago showed that although some preparations were effective, most of those examined were relatively inert, particularly those designed for use in dogs.[7] This doubtless explains much of the disrepute into which canine vaccination had fallen at that time. Subsequent work with potent phenolized vaccine has shown that a significant degree of protection can be obtained in dogs for a period of about a year with a single dose of vaccine, and a high degree of protection with three doses. Field tests have confirmed the practical value of such vaccination.[1]

Phenol, however, seems to be a relatively poor inactivating agent. There is evidence that more potent vaccine can be obtained by inactivation with formaldehyde, ether or chloroform. The best procedure at present, however, seems to be exposure to ultraviolet light. By freeing the virus suspension of solid particles and exposing it in a thin film to radiation from a lamp emitting rays of unusually short wave length, Levinson et al.[10] were able to inactivate the virus completely by an exposure of a fraction of a second. They found the vaccine much superior to phenolized vaccine made from the same virus suspension in antigenicity, uniformity and stability. This type is now available for general use, and eventually it may well supplant the older types of inactivated vaccine.

The second major problem concerns the paralytic accidents which may follow vaccination. Their frequency is variously stated, but it seems to be between one in 2000 [11] and one in 5000 cases,[9] with a mortality of about 15 per cent. These accidents may follow the administration of any of the vaccines hitherto used, and they may occur in individuals who had not actually been exposed to rabies. Although relatively rare, the risk of a protracted, disabling and possibly fatal illness is real and necessitates caution in the selection of cases for treatment. Those with wide experience in this field [12] believe that vaccine should be given only to those who have been actually bitten on bare skin or through torn clothing by an animal which is certainly or which presumably may have been rabid, or to small children who can not give a reliable account of the encounter and in whom paralytic accidents are much rarer than in adults. In the case of individuals who have merely handled a rabid animal, who show scratches from claws and not from teeth,

[10] Levinson, S. O., et al.: A new method for the production of potent irradiated vaccines with ultraviolet radiation, J. Immunol. **50**: 317–329, 1945.

[11] Remlinger, 1928, quoted by Bassoe, P., and Grinker, R. R.: Human rabies and rabies vaccine encephalitis, Arch. Neurol. and Psychiat. **23**: 1138–1160, 1930.

[12] Sellers, T. P.: Limitations of antirabic treatment, J. M. A. Georgia **35**: 132–133, 1946.

or who even have had saliva deposited on the skin (unless *fresh* open abrasions are present), the risk of paralytic accidents is greater than that of contracting rabies. Vaccine should never be administered merely to allay unreasonable panic in individuals casually exposed.

The risk of paralytic accidents is much greater in persons who have previously had a course of antirabies vaccine, and great caution should be used in treating them. Thus Sellers [12] reported that of seven cases of severe paralytic accidents (four fatal) occurring among 50,000 vaccinated individuals, five had had a previous course of antirabies vaccine. Five of these cases (three fatal) had been only casually exposed, and vaccine should not have been administered at all.

Although the pathogenesis of these paralytic accidents has not been conclusively demonstrated, there is now imposing evidence that they are not related to rabies virus but are manifestations of an allergic reaction to brain tissue present in the vaccine. Similar accidents have been observed infrequently after the administration of antirabies vaccine in dogs, mice and guinea pigs. Extensive degenerative changes ("encephalitis") histologically similar to those caused by antirabies vaccine have been produced in monkeys by repeated injections of heterologous or homologous brain tissue.[13, 14] This tendency is greatly increased if the material is mixed before injection with an adjuvant of the Freund type, a mixture of oils, various lipids and killed mycobacteria.[14] This procedure has been utilized by Habel [15] in guinea pigs to determine the capacity of various preparations of vaccine to produce such lesions. Kirk and Ecker [16] in two of five subjects receiving Semple vaccine, demonstrated complement fixing antibodies for normal brain tissue, which were in fairly high titer in one who reacted severely to the vaccine. Horack [17] has described the types of reaction to antirabies vaccine which may occur and has emphasized the part that allergy seems to play in their development.

Such observations naturally stimulated efforts to produce vaccine from which the troublesome antigenic factor was eliminated. Rabies virus can be grown in fluid cultures containing small fragments of living brain tissue. Such virus may retain a substantial degree of virulence, but in general this has tended to be variable and often low. Veeraraghaven [18] only has reported obtaining viral cultures of high virulence in cell-free media, but these results

[13] Rivers, T. M., and Schwentker, F. F.: Encephalitis accompanied by myelin destruction experimentally produced in monkeys, J. Exper. Med. **61**: 689–702, 1935.

[14] Kabat, E. A., et al.: Rapid production of acute disseminated encephalomyelitis in rhesus monkeys by injection of heterologous and homologous brain tissue with adjuvants, J. Exper. Med. **85**: 117–130, 1947.

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[17] Horack, H. M.: Allergy as factor in development of reactions to antirabic treatment, Am. J. M. Sc. **197**: 672–682, 1939.

[18] Veeraraghaven, N.: Cultivation of rabies virus in vitro, Nature **159**: 782, 1948.

are not generally accepted since attempts by others to confirm them have thus far been unsuccessful.

Koprowski [19] has succeeded in maintaining the virus in chick embryos. He used a special (Flury) strain of virus which had been adapted, first by serial passages through the brain of young chicks and subsequently through chick embryos by injections into the yolk sac. He found that the virus was present in all the tissues of the embryo and not limited to nervous tissue. Large doses injected intramuscularly in dogs did not produce rabies but did give a substantial immunity from subsequent injections of street virus.

The fact that fetal brain tissue does not cause the degenerative changes in the brain which follow repeated injections of adult brain suspension [14] led Chen-Jen and Zia [20] to carry two strains of fixed virus through a series of fetal guinea pigs by intracerebral injection in utero. The fetuses were delivered by operation four days later and suspensions of the brain were prepared. Such virus retained its virulence for mice, and formalinized vaccines prepared from it protected mice as effectively as did ordinary vaccine, both from the fetal strain and the original fixed strain.

Attempts have also been made to free ordinary vaccine from the antigenic factor present in brain tissue by chemical means. That of Habel [15] seems to have been successful. He first inactivated and partly purified the vaccine by extraction with benzene and ether. The virus was then precipitated from the suspension with a little calcium acetate, washed with water and then resuspended. Such virus did not produce encephalitis on injection into guinea pigs, although the original virus and the calcium acetate washings did so. Its antigenic power was "largely retained." "It is presumed that washed vaccines which no longer produce encephalitis in guinea pigs will likewise not produce postvaccinal encephalitis in man."

All of these procedures are still in the early experimental stage, but they obviously warrant further thorough investigation.

The present methods of treating human subjects who have been exposed to rabies are commonly regarded as highly effective. In the report of the results of antirabies vaccination during 1947 from the Pasteur Institute in Paris, where rabies is relatively well controlled, it is stated that no case of rabies in vaccinated individuals had been observed for 23 consecutive years. Few if any other Institutes can approach this record, however, and the Pasteur treatment as generally carried out is still open to improvement. There is, indeed, considerable indirect evidence that antirabies vaccine has little or no effect in those unfortunate victims who are so bitten that the incubation period is destined to be less than 30 days. This is especially frequent in small children and in those severely bitten about the face and

[19] Koprowski, H.: Experimental studies on rabies vaccine, Canadian J. Pub. Health **40**: 60–67, 1947.

[20] Chen-Jen, C., and Zia, S. H.: Studies on fixed virus propagated in the brain of the guinea pig fetus, J. Immunol. **60**: 17–21, 1948.

head. In this group the mortality from rabies is from six to 10 times that in vaccinated individuals as a whole.[9]

It has long been known that the administration of antirabies vaccine stimulates the production of neutralizing antibodies in the serum. Sporadic attempts have been made to utilize antisera in the management of rabies. These have had no curative effect whatever, but there is ground to hope that they might have prophylactic value if administered after a bite. Koprowski [19] has recently reported an experimental study of such sera in hamsters. Immune globulin obtained from antisera produced in rabbits by injections of virulent fixed virus was administered to hamsters following intramuscular inoculation with street virus. Substantial protective power was demonstrated if the serum was administered within 24 hours, but this fell rapidly to zero if treatment was delayed 72 hours or more. The degree of protection depended directly upon the relationship between the volume of serum and the quantity of virus administered. Koprowski believed that these results were so definite that a thorough field trial is fully warranted. There is no obvious reason why such antisera can not be perfected and produced on a large scale for general use, and there is good reason to hope that they will prove of great practical value, particularly in cases with a short incubation period in which no type of vaccine is ever likely to be effective.

Koprowski was unable to prevent rabies in these hamsters by administration of vaccines, even in "heroic" doses, if given after the inoculation of virus. This has been the result in the great majority of similar experiments with all types of laboratory animals. In a few instances, however, some degree of protection has been obtained if vaccine is administered in large doses, many times larger in proportion to body weight than those usually administered to man; e.g. Levinson et al.[10] in mice and Habel [8] in guinea pigs.

The prevention of rabies in man still depends primarily upon control of the disease in dogs. Effective measures for doing this are available, if carried out on a nation-wide basis, and the accomplishment of this now depends primarily upon educating the general public as to the importance of these measures and securing wide spread coöperation in their execution. The investigations of the past decade have provided a means of measuring precisely the antigenicity of antirabies vaccine and of providing vaccines of uniformly high potency. They promise to yield methods for eliminating the antigenic substances which cause the paralytic accidents. They may also provide immune sera which should supplement the effect of vaccine and in part compensate for the deficiencies of the Pasteur treatment, which are probably greater than is generally appreciated.

P. W. C.

REVIEWS

Applied Medicine. By G. E. Beaumont, M.A., D.M., F.R.C.P., D.P.H. 540 pages with 74 illustrations; 15.5 × 24 cm. The Blakiston Company, Philadelphia. 1950. Price, $6.00.

This is a delightful book which presents with great variety and in informal style a sampling of Dr. Beaumont's knowledge and wisdom acquired in over a quarter of a century of consulting practice. It is essentially a book of personal experience, and thus takes its place comfortably on the medical bookshelf beside such admirable works as Alvarez' *Nervousness, Indigestion and Pain,* and Ryle's *The Natural History of Disease.* Such books have the unique advantages of being unrestricted by a prescribed textbook syllabus and of containing just what the author is most interested in, knows best, and most wishes to talk about. They therefore contain the wheat of experience without the chaff.

This book is divided into four part. Part I, comprising 194 pages, is devoted to Descriptive Cases. The author presents and comments on cases he has handled which illustrate points of particular interest or practical value; about 40 cases are dealt with in this way. Part II, Short Notes on Cases, occupies only 37 pages, and deals briefly with limited aspects of a group of about 20 illustrated conditions. This section is often anecdotal in character and is perhaps the least valuable and instructive of the four sections, though by no means the least entertaining. Part III is probably the most valuable section of the book; comprising 274 pages it contains 24 case presentations and discussions at the bedside, demonstrated by Question and Answer. The last few pages of the book are devoted to Idle Thoughts, in which Dr. Beaumont has gathered together nearly 50 aphorisms, presumably accumulated from his own experience and added through the years to his medical doctrine.

Throughout the book there is a welcome emphasis on the symptoms experienced by the patient—"the reactions of the patient to his illness are as important as the observations of the physician." The text covers a good cross-section of the whole of medicine, and both common and rare diseases are given due consideration. Freely interspersed among the clinical discussions are interesting items of medical history and even of etymology. One is disappointed to find that with his obvious interest in the derivation of words, the author misspells miosis, pylephlebitis and achrestic; and that, of the few origins which have been printed in their Greek characters, two of these have been allowed to appear misprinted. The author perpetuates the misapprehension that an x-ray of the skull will exclude cysticercosis, ignoring the fact that, as Macarthur emphasizes, cysticerci in the brain usually do not calcify.

The book on the whole can be highly recommended. It covers a great deal of ground and is extremely readable. It offers perhaps the greatest opportunity to the student and young physician, for here he can browse and painlessly acquire considerable knowledge—knowledge tempered with a wisdom which comes only from long and wide experience. Some of the content may seem elementary to the older physician; but even he will derive pleasure and no little learning from many of these pages.

H. J. L. M.

Manual of Rheumatic Diseases. By W. Paul Holbrook, M.D., and Donald F. Hill, M.D., with the assistance of Charles A. L. Stephens, Jr., M.D. 182 pages; 14.5 × 21 cm. The Year Book Publishers, Inc., Chicago. 1950. Price, $4.25.

The third edition of this book is an up-to-date yet compact volume covering the more important and more common aspects of rheumatic diseases.

The first part of the book deals with the interrelationship of rheumatic diseases as well as the various etiological factors. The author then discusses the endocrinology and chemistry of these diseases, including a concise summary of cortisone and ACTH. The chapter on rheumatoid arthritis and allied entities and the chapter on fibrositis are most complete, yet retain a tendency toward terseness and the avoidance of superfluity.

The chapter on special treatments, I believe to be too inclusive to be of any great practical value. The bibliography at the end of the book seems rather complete for so small a volume, although it has not been checked.

For the student and the general practitioner, this book is ideal as basic training in the various common disorders classified as rheumatic.

L. A. K.

Renal Diseases. By E. T. Bell, M.D. 2nd Ed. 448 pages, with 123 illustrations and 4 color plates; 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1950. Price, $8.00.

This revised edition brings Dr. Bell's treatise on diseases of the kidney up to date. Few changes have been made since the first edition in 1946, the chief of these being amplification of the chapters on extrarenal azotemia and tubular diseases. Throughout the text relevant additions to the literature of the subject under discussion have been incorporated; in all this edition is longer than its forerunner by 14 pages.

After excellent introductory sections on the normal histology, and the normal and pathological physiology of the kidney, the developmental anomalies, hydronephrosis, glomerulonephritis, tubular diseases, extrarenal azotemia, pyelonephritis, diseases of the blood vessels, diseases of the kidney related to metabolic disorders, and tumors of the kidney, are dealt with in consecutive chapters. The whole text is excellently illustrated with microphotographs, and the writing is clear and of a high standard throughout.

Since the previous edition the author has reviewed 18,000 additional autopsies, and each subject is fully illuminated with his own experience and statistics as well as with abundant references to other authorities' work. Dr. Bell presents his own interpretation of the pathogenesis of acute glomerulonephritis, with which all investigators will not agree. In his discussion of this subject it is disappointing to the reviewer again to find no reference to the excellent contribution of Ellis. All observers will not subscribe to the interpretation of the pathogenesis of eclamptic convulsions (arteriolar spasm) which is supported by the author. Again, his concept of the relationship between subacute bacterial endocarditis and its several associated renal lesions, is not entirely in accord with that of other high authorities.

To single out for special praise any chapters of this admirable compilation would be invidious, although certain sections seem to be particularly well presented; among these may be mentioned that on the toxemias of pregnancy, and that on tubular disease. In the latter Dr. Bell rightly and strenuously opposes the introduction of the term "lower nephron nephrosis" as "a disservice to renal pathology in that it has added confusion instead of clarity."

The text deals for the most part with structural changes in the kidney, pathological physiology and clinical manifestations in renal diseases; the rationale of certain principles in therapy are, however, touched upon, though there is no attempt to present treatment in any detail. Apart from therapy, this book affords the most comprehensive and up-to-date treatise on renal diseases available today.

H. J. L. M.

Twentieth Century Mental Hygiene: New Directions in Mental Health. By MAURICE J. SHORE et al. 444 pages; 14 × 22.5 cm. Social Sciences Publishers, New York 23, N. Y. 1950. Price, $6.00.

This book covers a wide diversity of subjects pertaining to mental hygiene, written by various authors. From the point of view of the internist probably only several chapters will prove to be of interest. These include: Lloyd Thompson's "The Contribution of Mental Hygiene and the Future," in which is discussed the general concepts and workings of mental hygiene and some of its (idealistic) goals, a few of which are now partially realized. The latter include the influence and integration efforts of mental hygiene in the prenatal clinic, nursery school, regular school, colleges, community activities and armed services. Emphasis is placed on the importance of mental hygiene efforts early in the individual's life. In general the discussion deals with methods of infusing mental hygiene principles in many areas of life, which would help make for more social and emotional maturity. Dr. Edward A. Strecker's chapter on War Psychiatry and Its Influence gives his viewpoints in informative and interesting manner. In the section on psychology Max Hertzman's discussion on Rorschach provides a good basic concept of this most frequently used projective psychological test. The section on mental hygiene in other countries clearly emphasizes the need for attempting to resolve the more fundamental social difficulties before an effective mental hygiene program can be worked out. Much of the psychiatric orientation in these chapters is that of A. Myers, but with some reference to analytically oriented concepts, which probably represent the major trend in psychiatric thinking today. For example, Katzenelbogen, in discussing personality problems, expresses the view that environmental influences affect most potently early childhood, but remain effective throughout the life of the individual. Maurice Shore writes the opening and closing chapters, which many physicians would probably find too diffuse and philosophically theoretical.

The format of the book is somewhat irregular and confusing. For example, under the section War and Its Effects, are included chapters on mental hygiene and sex variants, and mental hygiene and industry.

In conclusion, while a great diversity of subjects are presented, they fall short of being of fairly high uniform quality but probably succeed in giving the reader a birdseye view, though hazy in spots, of the broad problems of mental hygiene.

H. W. N.

BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Advances in Internal Medicine. Volume IV. Editors: WILLIAM DOCK, M.D., Long Island College of Medicine, Brooklyn, New York, and I. SNAPPER, M.D., The Mount Sinai Hospital, New York, N. Y.; Associate Editors: TINSLEY R. HARRISON, M.D., Medical College of Alabama, Birmingham, Alabama; CHESTER S. KEEFER, M.D., Evans Memorial and Massachusetts Memorial Hospitals, Boston, Massachusetts; WARFIELD T. LONGCOPE, M.D., Cornhill Farm, Lee, Massachusetts, and J. MURRAY STEELE, M.D., Goldwater Memorial Hospital, New York University Division, Welfare Island, N. Y. 549 pages; 23.5 × 15.5 cm. 1950. Year Book Publishers, Inc., Chicago. Price, $10.00.

Cancer Services and Facilities in the United States, 1950. PHS Publication No. 14. 152 pages; 23.5 × 15 cm. (paper-bound). 1950. Federal Security Agency, Public Health Service, National Cancer Institute of the National Institutes of

Health, Bethesda, Maryland. Price, 35¢—for sale by the Superintendent of Documents, U. S. Government Printing Office, Washington-25, D. C.

Color Atlas of Pathology: Hematopoietic System; Reticulo-Endothelial System; Respiratory Tract; Cardiovascular System; Liver Alimentary Tract; Kidney and Urinary Tract; Musculoskeletal System. Prepared under the Auspices of the U. S. Naval Medical School of the National Naval Medical Center, Bethesda, Maryland. 546 pages; 25 × 18 cm. 1950. J. B. Lippincott Company, Philadelphia. Price, $20.00.

Diseases of the Tropics. By GEORGE CHEEVER SHATTUCK, M.D., Professor of Tropical Medicine, Harvard Medical School and Harvard School of Public Health, Emeritus, etc. 803 pages; 25.5 × 17 cm. 1951. Appleton-Century-Crofts, Inc., New York. Price, $10.00.

The External Secretion of the Pancreas. By J. EARL THOMAS, M.D., Professor of Physiology, Jefferson Medical College of Philadelphia. 149 pages; 22.5 × 14.5 cm. 1950. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $3.50.

Histamine Antagonists. By FREDERICK LEONARD and CHARLES P. HUTTRER, Warner Institute of Therapeutic Research, New York City. 122 pages; 25 × 17.5 cm. (paper-bound). 1950. National Research Council, Washington-25, D. C. Price, $1.50—copies may be obtained from the Publications Office, National Academy of Sciences, 2101 Constitution avenue, northwest, Washington-25, D. C.

Klinische Physiologie und Pathologie. By PROF. DR. FERDINAND HOFF. 782 pages; 25 × 17.5 cm. 1950. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 39.–

Methods in Medical Research. Volume 3. By RALPH W. GERARD, Editor-in-Chief; Genetics of Micro-organisms, S. E. LURIA, Editor; Assay of Neurohumors, J. H. GADDUM, Editor; Selected Psychomotor Measurement Methods, WALTER R. MILES, Editor; Methods for Study of Peptide Structure, CHOH HAO LI, Editor. Governing Board: IRVINE H. PAGE, Chairman; A. C. IVY, COLIN M. MACLEOD, CARL F. SCHMIDT, EUGENE A. STEAD, DAVID L. THOMSON. 312 pages; 22.5 × 14.5 cm. 1950. The Year Book Publishers, Inc., Chicago. Price, $7.00.

Methods in Medicine: The Manual of the Medical Service of George Dock, M.D., Sc.D., Formerly Professor of Medicine, Washington University School of Medicine; Formerly Physician-in-Chief, Robert A. Barnes Hospital, St. Louis; A Comprehensive Outline for Clinical Investigation, Management, and Treatment of Patients with Various Medical Disorders. Ed. 2. By GEORGE R. HERRMANN, M.D., Ph.D., Professor of Medicine, University of Texas Medical Branch at Galveston, etc. 488 pages; 23.5 × 15.5 cm. 1950. The C. V. Mosby Company, Saint Louis. Price, $7.50.

Pharmacological Basis of Penicillin Therapy. By KARL H. BEYER, Ph.D., M.D., F.A.C.P., Director of Pharmacological Research, The Medical Research Division, Sharp and Dohme, Incorporated, Glenolden, Pennsylvania. 214 pages; 22.5 × 14.5 cm. 1950. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $4.50.

Praktikum der Wichtigsten Infektionskrankheiten. By PROF. DR. C. HEGLER. 277 pages; 21 × 15 cm. 1950. George Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, New York. Price, $3.50.

Psychosomatics and Suggestion Therapy in Dentistry. By JACOB STOLZENBERG, D.D.S. 152 pages; 22 × 14 cm. 1950. Philosophical Library, New York. Price, $3.75.

Savill's System of Clinical Medicine, Dealing with the Diagnosis, Prognosis, and Treatment of Disease, for Students and Practitioners. Ed. 13. Edited by E. C. WARNER, M.D., F.R.C.P. 1198 pages; 22.5 × 14 cm. 1950. The Williams & Wilkins Company, Baltimore. Price, $7.00.

Toxaemias of Pregnancy, Human and Veterinary: A Ciba Foundation Symposium. Editors: JOHN HAMMOND, M.A., D.Sc., F.R.S.; F. J. BROWNE, M.D., D.Sc., F.R.C.S., F.R.C.O.G., and G. E. W. WOLSTENHOLME, O.B.E., M.B. 280 pages; 21.5 × 14 cm. 1950. The Blakiston Company, Philadelphia. Price, $4.50.

Urgent Diagnosis Without Laboratory Aid: A Discussion of the External Signs of Conditions Which Threaten Life. By PROF. DR. HANNS L. BAUR, a.o. Professor of Internal Medicine, University of Munich, etc. 89 pages; 22.5 × 14.5 cm. (limp leather binding). 1950. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $2.00.

When Minds Go Wrong: A Simple Story of the Mentally Ill—Past, Present and Future. By JOHN MAURICE GRIMES, M.D. 237 pages; 23.5 × 15.5 cm. 1949. Published and distributed by the author, 5209 South Harper Avenue, Chicago 15, Illinois. Price, $5.00.

COLLEGE NEWS NOTES

Nominations for A.C.P. Elective Offices, 1951–52

In accordance with provisions of the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1951–1952, are herewith announced to the Fellows and Masters of the College:

President-Elect ..... T. Grier Miller, Philadelphia, Pa.
First Vice President ..... LeRoy H. Sloan, Chicago, Ill.
Second Vice President ..... Walter B. Martin, Norfolk, Va.
Third Vice President ..... Howard P. Lewis, Portland, Ore.

Regular elections will take place at the 1951 Annual Session at St. Louis, Mo., April 12, 1951, the date of the Annual Business Meeting at the Kiel Municipal Auditorium, general headquarters.

The election of nominees shall be by the Fellows and Masters of the College. The above nominations do not preclude other nominations made from the floor at the Business Meeting.

Nominations of members of the Board of Regents and Board of Governors will be presented at the Business Meeting, as provided in the By-Laws.

Respectfully submitted,
Alex. M. Burgess, Sr., Providence, R. I.,
Chairman, *Committee on Nominations*

A.C.P. Regional Meetings

The following Regional Meetings of the American College of Physicians are scheduled for the early part of 1951. Others are under consideration and will be announced in due course.

Virginia Regional Meeting, Roanoke, February 28, 1951, Charles M. Caravati, F.A.C.P., Governor.

Kansas Regional Meeting, Wichita, March 16, 1951, William C. Menninger, F.A.C.P., Governor; William S. Middleton, F.A.C.P., Madison, Wis., President of the College, special guest speaker.

North Carolina Regional Meeting Held at Chapel Hill

The Annual Regional Meeting of the American College of Physicians for North Carolina was held at Chapel Hill, December 8, 1950, under the chairmanship of Dr. Harold J. Magnuson, F.A.C.P., of Chapel Hill, and the Governorship of Dr. Elbert L. Persons, F.A.C.P., of Durham. A very excellent scientific program was presented through the chairmanship of Dr. Luther W. Kelly, F.A.C.P., of the Program Committee. Dr. William S. Middleton, F.A.C.P., President of the College, delivered the chief address at the banquet, held at the Carolina Inn in the evening. Sixty-eight members of the College and forty-four guests were in attendance.

North Carolina was one of the early states to initiate regional meetings, first under the Governorship of the late Dr. Charles L. Minor and subsequently under the late Dr. Charles Hartwell Cocke and Dr. Paul F. Whitaker.

Kentucky Regional Meeting Held at Lexington

The Annual Regional Meeting of the American College of Physicians for Kentucky was held at Lexington, December 9, 1950, under the local chairmanship of Dr.

Charles N. Kavanaugh, F.A.C.P., and the Governorship of Dr. J. Murray Kinsman, F.A.C.P., Louisville. The scientific program was conducted at the Good Samaritan Hospital. Dr. Edward L. Bortz, F.A.C.P., Philadelphia, a Regent of the College, gave a paper on "The Biology of Aging" and addressed the banquet in the evening at the Lafayette Hotel on the activities of the College and its present objectives. Dr. William S. Middleton, F.A.C.P., Madison, Wis., President of the College, also addressed the banquet. Thirty-eight members and eighteen guests were in attendance. Next year the Regional Meeting will be held in Louisville, where a larger attendance is anticipated. Kentucky has held regional meetings of the College for many years.

The Midsouth Regional Meeting at Memphis

The States of Louisiana, Texas and Tennessee combined to hold an annual Regional Meeting at Memphis, Tenn., January 12–13, 1951, under the Governorship of Dr. William C. Chaney, with Dr. J. F. Hamilton acting as Chairman of Arrangements and Dr. L. Carl Sanders in charge of registration and hotel arrangements. The program was put on primarily by professors, associate professors and teachers in the medical schools of the University of Arkansas, Louisiana State University, Tulane University of Louisiana, University of Mississippi, University of Tennessee, Vanderbilt University, University of Texas, Southwestern Medical School and Baylor University. Dr. Willard O. Thompson, of Chicago, was the guest speaker on the scientific program. The program was marked by excellent papers of practical value. Dr. John B. Youmans, Dean of Vanderbilt University School of Medicine, was the Toastmaster at the banquet. Dr. William S. Middleton, Madison, Wis., President of the College, delivered the chief banquet address. Dr. James E. Paullin, of Atlanta, Ga., Dr. George Morris Piersol, Secretary-General of the College, of Philadelphia, and Mr. Edward R. Loveland, Executive Secretary of the College, Philadelphia, were among the special guests. "Colonel" Jack Major gave a humorous address entitled "Tomorrow Belongs to Our Children."

One hundred fifteen members of the College and 81 guests, making a total of 196, were in attendance. Miss Pearl M. Ott, Executive Assistant of the College, was in charge of registration. The 1952 Regional Meeting for that territory will be held in Texas or in Louisiana.

A.C.P. Annual Regional Meeting in Hawaii

The local group of members of the American College of Physicians in Honolulu held its annual meeting on January 5, 1951. The County Medical Society turned over its January meeting to the group, and the following program was presented:

"The Highlights of the A.C.P. Postgraduate Course, Peripheral Vascular Diseases Including Hypertension, given at the Mayo Clinic and Foundation, November 27–December 2, 1950." A. S. Hartwell, M.D., F.A.C.P.

"Diabetic Survey of Hawaii." Morton E. Berk, M.D. (Associate).

"Summary of Diagnoses of 10,000 Consecutive Medical Cases." N. P. Larsen, M.D., F.A.C.P.

"Dermatological Diagnoses in Hawaii." H. L. Arnold, Jr., M.D., F.A.C.P.

"Importance of Health Statistics." Mr. M. A. Taff.

"Weather in Relation to Allergy and Respiratory Disease." N. P. Larsen, M.D., F.A.C.P.

The meeting was well attended. Of special interest was the third paper. The diagnoses were made by twelve A.C.P. members who filled out a specially designed

card for each patient they saw, until they had a list of ten thousand consecutive cases. The cards were then tabulated on an IBM machine not only as to age, sex, race and diagnosis, but also as to the environment in which they lived; i.e., in Hawaii certain areas will have zero rainfall during a week while another area may have eight inches of rain.

Annals of Internal Medicine Available Through Microfilms

University Microfilms, 313 North First St., Ann Arbor, Mich., has been given the privilege of microfilming the Annals of Internal Medicine, thus making past volumes available through microfilm service to libraries and other agencies that desire to maintain reference libraries of the Annals with a minimum of storage space. Even though the film is prepared at a high reduction ratio, it is remarkably clear and sharp and when used with a reader giving enlargement of nineteen times or more, it is entirely satisfactory.

The first microfilm produced covers Volumes 30 and 31, year of 1949. The microfilms require a very minimal amount of space for storage, being contained in a small cardboard box about two inches square.

New Life Members—The American College of Physicians

The College is gratified to announce that the following Fellows have become Life Members of the American College of Physicians, since the publication of the last issue of this journal:

Dr. J. W. McMeans, Florence, S. C.
Dr. Joseph Levy, New Rochelle, N. Y.
Dr. Frank Lamberta, Jamaica, N. Y.
Dr. W. Taliaferro Thompson, Jr., Richmond, Va.
Dr. George N. Thompson, Los Angeles, Calif.
Dr. John Eiman, Abington, Pa.
Dr. Kurt Berliner, New York, N. Y.
Dr. Irving E. Steck, Chicago, Ill.
Dr. William E. Hill, Naugatuck, Conn.
Dr. Cecil C. Dustin, Rochester, N. H.
Dr. Orville E. Egbert, El Paso, Tex.
Dr. Joseph Spurgeon Hiatt, Jr., McCain, N. C.
Dr. Matthew T. Moore, Phila., Pa.
Dr. William Strange Norton, II, New York, N. Y.
Dr. Harold A. Rosenbaum, Chicago, Ill.
Dr. Francis J. Scully, Hot Springs National Park, Ark.
Dr. William B. Terhune, New Canaan, Conn.
Dr. Albert Vander Kloot, Chicago, Ill.
Dr. Harry F. Wechsler, New York, N. Y.
Dr. Ruth Walker Wilson, Beaver, Pa.
Col. Forrest R. Ostrander, South Mountain, Pa.

Gifts to the College Library of Publications by Members

The following Fellows of the College have recently presented copies of their new books to the College Library of Publications by Members:

Dr. Benjamin V. White, Hartford, Conn., "Diagnosis in Daily Practice" (with Charles F. Geschickter, M.D.).

Dr. Roscoe L. Pullen, New Orleans, La., "Medical Diagnosis," Second Edition, and "Communicable Diseases."

The College Library of Publications by Members is maintained at College Headquarters. Members frequently present copies of their books to the College and the library has become a living memorial to the member-authors.

U. S. Public Health Service Communicable Disease Center Offers Laboratory Training Courses

The United States Public Health Service Communicable Disease Center at Chamblee, Ga., has announced an extensive schedule of Laboratory Training Courses to be given between January 1 and December 31, 1951. Courses for the most part are of one- and two-weeks' duration, although a few are for three or four weeks. Subjects of different courses include, among others: Laboratory Diagnosis of Syphilis; Laboratory Diagnosis of Bacterial Diseases; Laboratory Diagnosis of Parasitic Diseases; Laboratory Diagnosis of Enteric Diseases; Laboratory Diagnosis of Mycotic Diseases; Laboratory Diagnosis of Tuberculosis; Laboratory Diagnosis of Virus Diseases; Laboratory Diagnosis of Rabies; Clinical Chemistry.

Information and application forms may be obtained from the Officer-in-Charge, Laboratory Training Services, Communicable Disease Center, U. S. Public Health Service, P. O. Box 185, Chamblee, Ga.

National Foundation Fellowships

The National Foundation for Infantile Paralysis has announced the availability of a limited number of predoctoral and postdoctoral fellowships to candidates whose interests are research and teaching in the fields related to the problems of poliomyelitis such as virology, biochemistry, biophysics, orthopedics, pediatrics, neurology and epidemiology. Stipends to fellows will range from $1200–$1800 a year plus tuition for the predoctoral level, to $3600–$7000 a year for the postdoctoral level. Institutions which accept fellows will receive additional compensation. Complete information concerning qualifications and applications may be obtained from: Division of Professional Education, National Foundation for Infantile Paralysis, 120 Broadway, New York 5, New York.

CARE Aid Urged for Korea

CARE is appealing for funds to send relief packages from Americans to war-devastated Korea, whose people are in desperate need of food and clothing.

Contributions in any amount sent to CARE for Korea, 20 Broad St., New York 5, N. Y., or any local CARE office in this country, will be used by the non-profit agency to deliver gift packages, in the name of the donors, to destitute Korean families chosen on the basis of greatest need.

Six types of CARE packages are available: Food, underwear and socks, or woolen suiting, at $10 each; knitting wool, $13; woolen blanket and cotton fabrics, $7 each. Contributions less than the cost of a complete package will be pooled. All donors will receive a CARE receipt.

The CARE campaign was undertaken at the request of the Advisory Committee on Voluntary Foreign Aid of the U. S. Department of State and has been endorsed by President Truman.

Dr. William S. McCann, F.A.C.P., Rochester, N. Y., a Regent of the College, was recently appointed to the Committee on Medical Sciences of the Department of Defense Research and Development Board.

Dr. Thomas P. Murdock, F.A.C.P., Meriden, Conn., a member of the American Medical Association's Board of Trustees, was guest of honor at a testimonial dinner in New Haven on November 29, in recognition of his many years of service to the [illegible] profession. Among the speakers was Dr. Louis H. Bauer, F.A.C.P., New York, N. Y., Chairman of the American Medical Association's Board of Trustees.

Among the guest speakers at the Twentieth Annual Spring Clinical Conference of the Dallas Southern Clinical Society, which will be held March 26–27, will be Dr. Dickinson W. Richards, Jr., F.A.C.P., New York, N. Y., Dr. Francis E. Senear, F.A.C.P., Chicago, Ill., and Dr. William A. Sodeman, F.A.C.P., New Orleans, La.

Dr. G. Howard Gowen, F.A.C.P., Springfield, Ill., Deputy Director of the Division of Hospitals and Chronic Illness of the Illinois Department of Public Health, was elected President of the Public Health Cancer Association of America at its annual meeting in October, 1950.

Dr. Walter M. Boothby, F.A.C.P., a Professor Emeritus of the Mayo Foundation, has joined the professional staff of the School of Aviation Medicine, Randolph Field, Texas, as research adviser. For the past two years Dr. Boothby has been adviser on research in aviation medicine and physiology to the Swedish Aviation Medicine Council at the University of Lund.

Dr. Ellison R. Cook, III, (Associate), Savannah, Ga., has just been named Savannah's "Outstanding Young Man for the Year 1950" by the Junior Chamber of Commerce. This honor was conferred on Dr. Cook at the Annual Founder's Day Banquet and was made in recognition of his "unselfish community work in establishing the heart clinic at the Community Health Center, and as medical advisor to the Savannah Chapter of the American Red Cross."

Among the speakers at the International Post-Graduate Medical Assembly of Southwest Texas, which was held in San Antonio, January 23–25, were Dr. Keith J. R. Wightman, F.A.C.P., Toronto, Ont., Canada, who spoke on "Clinical Disturbances of Fat Absorption," and Dr. Oscar Swineford, Jr., F.A.C.P., Charlottesville, Va., whose subject was "ACTH and Cortisone in Allergic Diseases."

At the annual meeting of the American Society for the Study of Arteriosclerosis which was held in Chicago, Ill., in November, 1950, Dr. E. Cowles Andrus, F.A.C.P., Baltimore, Md., was installed as President.

Dr. Jean A. Curran, F.A.C.P., Brooklyn, N. Y., has been appointed Dean of the State University Medical Center at New York City, College of Medicine, which was formerly the Long Island College of Medicine. Dr. Curran has been associated with the college since 1937, having served both as Dean and as President.

E. R. Squibb & Sons, New York, N. Y., has announced the appointment of Dr. William A. Feirer, F.A.C.P., to the newly created post of Vice President in Charge of Scientific Affairs. For the past several years Dr. Feirer has been Executive Vice President of Sharp & Dohme.

OBITUARY

DR. GEORGE PEYTON PRATT

George Peyton Pratt, M.D., F.A.C.P., was born in Lincoln, Nebr., May 5, 1888, and died in Omaha, Nebr., December 19, 1950, following a lingering illness.

Dr. Pratt received his B.S. degree in 1910 from the University of Nebraska and his M.D. degree in 1913 from Rush Medical College. Following the completion of his internship at Cook County Hospital, Chicago, in 1915, he opened his practice in Omaha. He was appointed Clinical Assistant in Genito-Urinary Diseases at the University of Nebraska College of Medicine in 1915. He was appointed Instructor in Medicine in 1917, Assistant Professor in 1922, Associate Professor in 1934, Professor in 1939, and Emeritus Professor of Clinical Medicine in 1948.

During World War I he was Lieutenant in the Medical Corps, U. S. Army, A. E. F., being Chief Internist for Evacuation Hospital No. 1.

He contributed to various medical journals articles on internal medicine subjects and was Editor of the University of Nebraska Number of the Medical Clinics of North America, Vol. 12, No. 2, September 1928.

Dr. Pratt was a Fellow of the American Medical Association and component societies, the Omaha Mid-West Clinical Society, Fellow of the American College of Physicians since 1922, and Diplomate of the American Board of Internal Medicine since 1937. He was a member of Beta Theta Pi and Nu Sigma Nu fraternities.

He was a member of the medical staffs of the Immanuel Deaconess Institute, the Nebraska Methodist Hospital, the University of Nebraska Hospital, the Bishop Clarkson Memorial Hospital and the Lutheran Hospital.

Survivors are a son, Dr. Peyton Pratt, of Omaha, and two sisters, Mrs. M. A. Shaw of David City, Nebraska, and Mrs. Calvin Webster, of Tucson, Arizona.

Dr. Pratt will be long remembered by the many who are now practicing physicians as a brilliant teacher and kindly adviser. The Faculty of the University of Nebraska College of Medicine, as well as the community at large, has suffered an irreparable loss in his passing.

J. D. McCarthy, M.D., F.A.C.P.,
Governor for Nebraska

PROGRAM

THE AMERICAN COLLEGE OF PHYSICIANS

Thirty-second Annual Session

ST. LOUIS, MO.

April 9–13, 1951

GENERAL SESSIONS AND LECTURES

William S. Middleton, Madison, Wis., President

GENERAL CHAIRMAN

Ralph A. Kinsella, St. Louis, Mo.

COMMITTEE ON ARRANGEMENTS

Ralph A. Kinsella, Chairman

Harry L. Alexander
Goronwy O. Broun
Mrs. Anthony B. Day
Alfred Goldman
Paul O. Hagemann
Alphonse McMahon
Carl V. Moore
Raymond O. Muether
Daniel L. Sexton
W. Barry Wood, Jr.

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Joseph C. Edwards
Frank R. Finnegan
David B. Flavan
William C. MacDonald
James P. Murphy
Algie R. Shreffler

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Carl V. Moore, Co-Chairman

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Anthony B. Day, St. Luke's Hospital
Joseph V. Finnegan, Firmin Desloge Hospital
Robert J. Glaser, St. Louis City Hospital (Washington University Service)
Samuel B. Grant, Missouri Baptist Hospital
Robert C. Kingsland, Veterans Administration Hospital, Jefferson Barracks
William A. Knight, Jr., St. Louis City Hospital (St. Louis University Service)
Carl V. Moore, Barnes Hospital

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Sim F. Beam
Leon Bromberg
Michael M. Karl
James R. Nakada
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Sedgwick Mead
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William H. Olmsted
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Herbert C. Sweet

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George Morris Piersol, Chairman

Garfield G. Duncan
Thomas Klein

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Mrs. Ralph A. Kinsella, Honorary Chairman
Mrs. Anthony B. Day, Chairman

Mrs. Harry L. Alexander
Mrs. Goronwy O. Broun
Mrs. O. P. J. Falk
Mrs. David B. Flavan
Mrs. Paul O. Hagemann
Mrs. Bruce D. Kenamore
Mrs. Ernest H. Parsons
Mrs. David M. Skilling, Jr.
Mrs. W. Barry Wood, Jr.

GENERAL INFORMATION

GENERAL HEADQUARTERS

Kiel Auditorium
St. Louis, Mo.

Registration headquarters, the information bureau, technical exhibits, general sessions, morning lectures, panel discussions, televised clinics, meetings of committees, of the Board of Regents and of the Board of Governors. The Annual Convocation and the Annual Banquet will take place in the Jefferson Hotel.

HOTEL ACCOMMODATIONS

A fully adequate number of first-class guest rooms has been reserved, and a Housing Bureau, working through the Committee on Hotels and Transportation, has been set up at the Hotels Convention Reservation Bureau, A.C.P., Room 406, 911 Locust Street, St. Louis 1, Mo. Applications for rooms should be made to this Bureau, preferably on the official form provided by the College, but in the absence of the form, the Bureau will handle letters of application, provided the applicant identifies himself with the College and its Annual Session. It is requested that three choices of hotels be indicated, and that a reasonable range of rates be shown. Whenever possible, arrangements should be made for occupancy of rooms accommodating two persons. Confirmation from the hotel where the reservation has been made will be mailed to each applicant. If, after making reservations, the applicant finds it impossible to attend, he is requested to notify the Hotels Convention Reservation Bureau promptly so that his accommodations may be made available to another physician. Application blanks for housing accommodations may be obtained by writing to: Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

LIST OF HOTELS

Hotel	For One Person	For Two Persons		2-Room Suites Parlor and Bedroom
		Double Bed	Twin Beds	
American	$3.50–$6.00	$4.50–$7.00	$5.50–$7.50	$8.00
Baltimore	3.50– 4.50	5.50– 6.50	6.50	7.50– 12.00
Chase	4.50– 8.00	7.00–10.00	8.00–11.00	12.00– 30.00
Claridge	3.50– 6.00	5.50– 8.00	7.00– 9.00	12.00 & up
DeSoto	3.75– 5.25	5.75– 9.00	7.25–14.00	12.00– 20.00
Forest Park	3.75– 5.50	5.50– 8.00	7.00 & up	12.00– 15.00
Jefferson	4.50– 7.00	6.25– 8.50	8.00– 9.00	13.00– 24.00
Kings-Way	3.00– 4.50	4.50– 6.75	8.00	8.50– 12.00
Lennox	4.00– 7.00	5.50– 8.50	7.75– 8.50	13.00
Majestic	3.00– 4.25	4.75– 6.00	6.25– 8.00	
Mark Twain	3.75– 5.50	6.00– 7.50	7.50– 8.50	
Mayfair	4.00– 8.50	5.00– 7.50	7.75– 8.50	14.00 & up
Melbourne	3.75– 5.50	6.50– 8.50	8.00– 9.50	12.50– 18.00
Park Plaza	6.00–10.00	9.00–13.00	9.00–13.00	13.00 & up
Roosevelt	4.00– 5.75	5.75– 8.25	6.75– 8.25	
Sheraton	4.00– 9.85	6.00– 9.85	8.85–12.85	10.00– 30.00
Statler	4.00– 7.00	6.00– 9.00	8.50–14.00	22.00– 23.50
Warwick	2.75– 3.50	4.00– 5.00	6.00	
York	2.75– 4.50	4.50– 6.00	5.50– 7.00	

Who May Register—

(*a*) All members of the American College of Physicians in good standing for 1951.

(*b*) All newly elected members.

(*c*) Graduate medical students pursuing courses in local institutions of St. Louis, including residents in St. Louis hospitals, without registration fee, **upon presentation of matriculation cards or other evidence of registration at these institutions**; admission to exhibits, general sessions, morning lectures and TV clinics.

(*d*) Members of the staff, including interns, of the St. Louis hospitals participating in the program, without registration fee, **upon presentation of proper identification**; admission to exhibits, general sessions, morning lectures and TV clinics (this does not include courtesy staff members).

(*e*) Members of the Medical Corps of the Army, Navy, Public Health Service, Air Force and Veterans Administration, either of the United States or Canada, without registration fee, **upon presentation of proper credentials.**

(*f*) Qualified physicians who may wish to attend this Session as visitors, sponsored in advance by letter or in person by a member of the College; such physicians shall pay a registration fee of $25.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published) included within such fee.

The above regulations are essential because of the increasingly large attendance at the Annual Sessions of the College, and the necessity of accommodating members first.

Registration Bureau—While official registration will start on Monday morning, April 9, advance registration of members and exhibitors will be provided for on Sunday, April 8, from 2:30 to 5:00 in the afternoon. The Registration Bureau, located in Kiel Auditorium near the entrance to the Arena on 15th Street, will be open through the week from 8:30 A.M. to 5:45 P.M.

Registration Blanks for all Clinics, Clinico-Pathological Conferences and Panel Discussions will be sent with the individual program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

Bulletin Board for special announcements will be located near the Registration Bureau at the Kiel Auditorium.

Transportation—Local transportation arrangements are in charge of the Committee on Hotels and Transportation which will issue full information at the meeting.

The General Business Meeting of the College will be held from 2:00 to 2:40 P.M., Thursday, April 12, immediately preceding the afternoon scientific session. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, and the annual reports of the Secretary-General, Executive Secretary and Treasurer will be received. The President-Elect, Dr. Maurice C. Pincoffs, Baltimore, Md., will be inducted into office.

Board and Committee Meetings—All meetings will be held at the Kiel Auditorium. Special meetings will be announced and posted.

A Dinner Meeting of the Board of Regents and of the Board of Governors will be held at the Jefferson Hotel, Sunday, April 8, 7:00 P.M.

Committee on Credentials

Saturday, April 7, 10:00 A.M., Executive Secretary's Office, Kiel Auditorium

Joint Meeting Board of Regents and Board of Governors

Sunday, April 8, 2:00 P.M., Room 3-B, Kiel Auditorium

Board of Regents

*Tuesday, April 10, 12:00 M., Room 3-B, Kiel Auditorium
*Friday, April 13, 12:00 M., Room 3-B, Kiel Auditorium

* Buffet luncheon served.

Board of Governors

*Wednesday, April 11, 12:00 M., Room 3-B, Kiel Auditorium

Other Committee meetings will be announced in the formal program and also posted on the Bulletin Boards of the Jefferson Hotel and the Kiel Auditorium.

SPECIAL FEATURES

The Annual Convocation and the President's Reception, Wednesday, April 11, 8:30 P.M.—The Annual Convocation of the College will be held in the Gold Room of the Jefferson Hotel. All members of the College and their families, and those of the public who are interested, are cordially invited. No tickets are required. All Physicians elected Fellows of the College since the 1950 Convocation, and all previously elected Fellows who have not been formally inducted, should be present. They, together with Officers, Regents and Governors of the College, are requested to assemble in the Crystal Room (across the corridor to the rear of the Gold Room) at 7:45 P.M., preparatory to the formation of the procession.

The Convocation ceremony will include the President's address, "The Destiny of The American College of Physicians," and the Convocational Oration, "The Patient and the Physician," by Sir John Parkinson of London, England. The James D. Bruce Memorial Medal for 1951 and the Alfred Stengel Diploma will be awarded. Recipients of Research Fellowships and of Latin-American Fellowships of the College for 1951 will be announced, an Honorary Fellowship will be conferred upon our English guest, and a Mastership will be conferred upon a distinguished member of the College. The class of new Fellows will be inducted by the President.

Following the Convocation, the President's Reception will be held in the Ivory Room, and the dance will take place in the Gold Room.

The Annual Banquet, Thursday, April 12, 8:00 P.M.—The Banquet will be held in the Gold Room of the Jefferson Hotel. A gala occasion, with excellent food, good fellowship and fine entertainment, is being planned. Watch the final program for details. Table reservations for groups may be arranged.

Entertainment of Visiting Women—The Ladies' Entertainment Committee of St. Louis extends a cordial welcome to the wives of the members of the College to the 1951 meeting. Due to world conditions and mobilization, it does not seem advisable to pursue the formal program of entertainment features for the visiting ladies as has been customary in the past. Hostesses will be available during registration hours to help the ladies plan the things in which they are particularly interested. The Ladies' Headquarters in the Jefferson Hotel will supply lists of current events, places to go and things to see, shopping and restaurant information. The Committee is anxious to assist you in locating friends and spending your time enjoyably.

On Tuesday, April 10, the St. Louis Ladies' Entertainment Committee cordially invites all the visiting ladies to be its guests at a Reception and Tea from 3:00 to 5:00 in the Tiara Lounge of the Park Plaza Hotel, and sincerely hopes that all the visiting ladies will plan to attend. With the final program a reservation card will be enclosed.

Registration hours at the Jefferson Hotel will be as follows:
Sunday, April 8—2:00 to 5:00 P.M.
Monday, April 9, through Wednesday, April 11—9:30 A.M. to 5:00 P.M.
Thursday, April 12—9:30 A.M. to 3:00 P.M.
Program:
Tuesday, April 10, 3:00 P.M.—Reception and Tea, The Tiara Lounge, Park Plaza Hotel.

*Buffet luncheon served.

Wednesday, April 11, 8:30 P.M.—Convocation, President's Reception and Dance, Jefferson Hotel.

Thursday, April 12, 7:00 P.M.—"Dutch Treat" Cocktail Party, Ivory Room, Jefferson Hotel.

8:00 P.M.—Annual Banquet of the College, Gold Room, Jefferson Hotel.

Special Trains and Post-Convention Activities—No official arrangements have been concluded for complete special trains, but, in some localities, College Governors may sponsor special cars on certain trains to St. Louis and return. Members are advised to consult the Governors for their states concerning any special car or travel arrangements.

The Baltimore & Ohio Railroad has been granted permission to arrange special service from the East, and, in conjunction with other railroads, to set up advantageous schedules from other parts of the country. In conjunction with Pan-American Airlines, the B. & O. R. R. is making available a most interesting post-convention tour by air to Mexico City and environs. Schedules and details may be obtained from Mr. Arthur Purner, Baltimore & Ohio R. R., Broad & Walnut Sts., Philadelphia, Pa.

Color Television of Medical Clinics—Through the courtesy of Smith, Kline & French Laboratories, Philadelphia, and the co-operation of the Columbia Broadcasting System, the College will have again an interesting and unique program of clinics televised in color to the headquarters, the Kiel Auditorium at St. Louis, 9:30 to 11:30 A.M., daily, Tuesday through Friday. Color television is an innovation that cannot help but revolutionize medical education. The great success of our first color television program at the Boston Session in 1950 gave this year's program committee confidence and assurance to continue and extend the program at St. Louis. Smith Kline & French have performed a great service to physicians for making possible such programs at medical gatherings all over the country. They introduced color television as a medical teaching aid at the American Medical Association meeting in Atlantic City in 1949; over 137,000 medical men have viewed the programs; more than 400 separate medical clinics and surgical operations have been televised in this period.

THE TECHNICAL EXHIBIT

The Technical Exhibit will be located in the Arena of the Kiel Auditorium and promises to be one of the most attractive and all-inclusive exhibits ever conducted by the College. The Committee on Exhibits maintains the highest possible standards in the conduct of this Exhibit. Exhibitors are admitted only by invitation; irrelevant exhibits are eliminated and only firms which present a group of approved products of scientific interest to the internist and allied specialist may exhibit.

Members and guests of the College are encouraged to give the exhibitors their courteous and interested attention, thus recognizing their contributions to the meeting and the effort they make and the expense to which they go in building superior displays and furnishing, freely, valuable scientific information.

The Exhibits will be open from 8:30 A.M. to 5:45 P.M. daily from Monday through Thursday, and from 8:30 A.M. to 2:30 P.M. on Friday. Intermissions have been arranged providing additional time for the inspection of Exhibits.

1951 EXHIBITORS

Abbott Laboratories, North Chicago, Ill.
Aloe Company, A. S., St. Louis, Mo.
American Hospital Supply Corporation, Evanston, Ill.
American Journal of Medicine, Inc., The, New York, N. Y.
Ames Company, Inc., Elkhart, Ind.

Appleton-Century-Crofts, Inc., New York, N. Y.
Armour Laboratories, The, Chicago, Ill.
Association of American University Presses, New York, N. Y.
Ayerst, McKenna & Harrison Limited, New York, N. Y.

Baum Co., Inc., W. A., New York, N. Y.
Becton, Dickinson & Co., Rutherford, N. J.
Bilhuber-Knoll Corp., Orange, N. J.
Bischoff Company, Inc., Ernst, Ivoryton, Conn.
Blakiston Company, The, Philadelphia, Pa.
Bristol Laboratories, Inc., New York, N. Y.
Burroughs Wellcome & Co. (U. S. A.) Inc., Tuckahoe, N. Y.

Cambridge Instrument Co., Inc., New York, N. Y.
Carnation Company, Los Angeles, Calif.
Chilcott Laboratories—The Maltine Company, Morris Plains, N. J.
Chilean Iodine Educational Bureau, Inc., New York, N. Y.
Ciba Pharmaceutical Products, Inc., Summit, N. J.
Collins, Inc., Warren E., Boston, Mass.
Commercial Solvents Corporation, New York, N. Y.

Davies, Rose & Company, Limited, Boston, Mass.
Davis Company, F. A., Philadelphia, Pa.
Devereux Schools, Devon, Pa., and Santa Barbara, Calif.
DeVilbiss Company, The, Toledo, Ohio
Dietene Company, The, Minneapolis, Minn.
Doak Company, Inc., Cleveland, Ohio
Doho Chemical Corporation, New York, N. Y.

Edin Company, Inc., Worcester, Mass.
Electro-Physical Laboratories, Inc., Rye, N. Y.

Fleet Co., Inc., C. B., Lynchburg, Va.
Flint, Eaton & Company, Decatur, Ill.

General Electric X-Ray Corporation, Milwaukee, Wis.
Gerber Products Company, Fremont, Mich.
Gradwohl Laboratories, St. Louis, Mo.
Grune & Stratton, Inc., New York, N. Y.

Harrower Laboratory, Inc., The, Jersey City, N. J., and St. Louis, Mo.
Heinz Company, H. J., Pittsburgh, Pa.
Hoeber, Inc., Paul B., New York, N. Y.
Hoffmann-La Roche, Inc., Nutley, N. J.
Hollister-Stier Laboratories, Wilkinsburg, Pa., Spokane, Wash., and Los Angeles, Calif.

Ives-Cameron Company, Inc., New York, N. Y.

Jones Metabolism Equipment Co., Chicago, Ill.
"Junket" Brand Foods Division, Chr. Hansen's Laboratory, Inc., Little Falls, N. Y.

Kinney & Company, Columbus, Ind.

Lea and Febiger, Philadelphia, Pa.
Lederle Laboratories Division, New York, N. Y.
Leitz, Inc., E., New York, N. Y.

Lilly and Company, Eli, Indianapolis, Ind.
Lippincott Company, J. B., Philadelphia, Pa.

M & R Laboratories, Inc., Columbus, Ohio
Macmillan Company, The, New York, N. Y.
Mallon Chemical Corporation, New York, N. Y.
McNeil Laboratories, Inc., Philadelphia, Pa.
Mead Johnson & Company, Evansville, Ind.
Medco Products Co., Tulsa, Okla.
Medical Bureau, The, Chicago, Ill.
Medical Film Guild, Ltd., New York, N. Y.
Merck & Co., Inc., Rahway, N. J.
Merrell Company, The Wm. S., Cincinnati, Ohio
Mosby Company, The C. V., St. Louis, Mo.

National Drug Company, The, Philadelphia, Pa.
Nelson & Sons, Thomas, New York, N. Y.
Nepera Chemical Co., Inc., Yonkers, N. Y.

Oxford University Press, Inc., New York, N. Y.

Parke, Davis & Company, Detroit, Mich.
Pfizer & Co., Inc., Chas., Brooklyn, N. Y.

Ralston Purina Company, St. Louis, Mo.
Robins Company, Inc., A. H., Richmond, Va.
Rystan Company, Inc., Mount Vernon, N. Y.

Sanborn Company, Cambridge, Mass.
Sandoz Chemical Works, Inc., New York, N. Y.
Saunders Company, W. B., Philadelphia, Pa.
Schenley Laboratories, Inc., Lawrenceburg, Ind.
Schering Corporation, Bloomfield, N. J.
Searle & Co., G. D., Chicago, Ill.
Sharp & Dohme, Inc., Philadelphia, Pa.
Smith, Kline & French Laboratories, Philadelphia, Pa.
Squibb & Sons, E. R., New York, N. Y.
Swift & Company, Chicago, Ill.

U. S. Vitamin Corporation, New York, N. Y.
Ulmer Pharmacal Company, Minneapolis, Minn.
Upjohn Company, The, Kalamazoo, Mich.

Vanpelt & Brown, Inc., Richmond, Va.
Varick Pharmacal Co., Inc., New York, N. Y.

Wallace & Tiernan Products, Inc., Belleville, N. J.
Warner & Company, Inc., William R., New York, N. Y.
Warren-Teed Products Company, The, Columbus, Ohio
Westinghouse Electric Corporation, Pittsburgh, Pa.
White Laboratories, Inc., Newark, N. J.
Williams & Wilkins Company, The, Baltimore, Md.
Winthrop-Stearns, Inc., New York, N. Y.
Woodward Medical Personnel Bureau, Chicago, Ill.
Wyeth Incorporated, Philadelphia, Pa.

Year Book Publishers, Inc., The, Chicago, Ill.

OUTLINE OF THE ST. LOUIS SESSION

Bold Type indicates events at Kiel Auditorium

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	April 9	**April 10**	**April 11**	**April 12**	**April 13**
9:15 A.M. to 11:30 A.M.	Morning free **Registration, Exhibits, etc.**	Hospital Clinics **Color Televised Clinics**	**Morning Lectures Color Televised Clinics**	Hospital Clinics **Color Televised Clinics**	**Morning Lectures Color Televised Clinics**
12:00 M. to 1:15 P.M.		**Panel Discussions**	**Panel Discussions**	**Panel Discussions**	**Panel Discussions**
2:00 P.M. to 5:00 P.M.	**1st General Session**	**2nd General Session**	**3rd General Session**	**Annual Business Meeting 4th General Session**	**5th General Session**
Evening			7:45 Pre-Convocation Assembly 8:30 Convocation 10:15 President's Reception and Ball	8:00 Banquet	

GENERAL SESSIONS PROGRAM

Opera House, Kiel Auditorium

FIRST GENERAL SESSION

Monday Afternoon, April 9, 1951

Presiding Officer

Ralph A. Kinsella, F.A.C.P., St. Louis, General Chairman

P.M.

2:00 Addresses of Welcome:

The Honorable JOSEPH M. DARST, Mayor of St. Louis.
LEROY SANTE, M.D., F.A.C.P., President, St. Louis Medical Society.
ROBERT MOORE, M.D., Dean, Washington University School of Medicine.
MELVIN CASBERG, M.D., Dean, St. Louis University School of Medicine.

Response to Addresses of Welcome:

WILLIAM S. MIDDLETON, F.A.C.P., President, The American College of Physicians.

Presiding Officer

President William S. Middleton, F.A.C.P., Madison, Wis.

2:30 The James D. Bruce Memorial Lecture on Preventive Medicine: Preventive Immunization in a National Emergency.

ROLLA EUGENE DYER, M.D. (by invitation), Director of Research, Emory University; Assistant Surgeon General, U. S. Public Health Service (retired); Former Director, National Institutes of Health; Atlanta, Ga.

3:00 The Clinician, An Obituary.

HORACE M. KORNS, F.A.C.P., Iowa City.

3:20 Cardiac Symptoms.

SIR JOHN PARKINSON, F.R.C.P. (London), London, England.

3:50 INTERMISSION.

4:10 Nutritional Factors in Cardiac Disease.

THOMAS M. DURANT, F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine.

4:30 The Place of the Electrocardiogram in Cardiac Diagnosis.

FRANCIS F. ROSENBAUM, F.A.C.P., Assistant Clinical Professor of Medicine, Marquette University School of Medicine.

4:50 Observation on the Results of Subtotal Adrenalectomy in Severe, Otherwise Intractable Hypertension.

CHARLES C. WOLFERTH, F.A.C.P., Professor of Medicine, University of Pennsylvania School of Medicine.

5:10 ADJOURNMENT.

SECOND GENERAL SESSION

Opera House, Kiel Auditorium

Tuesday Afternoon, April 10, 1951

Presiding Officer
Maurice C. Pincoffs, M.A.C.P., Baltimore, Md.

P.M.

2:00 **Hepatic Amebiasis.**
WILLIAM A. SODEMAN, F.A.C.P., Professor of Preventive Medicine, Tulane University of Louisiana School of Medicine.

2:20 **Allergy in the Aged.**
RICHARD A. KERN, F.A.C.P., Professor of Medicine and Head of the Department, Temple University School of Medicine.

2:40 **The Effect of Prolonged Administration of Thyroid.**
RAY F. FARQUHARSON, F.A.C.P., F.R.C.P. (Canada), Professor of Medicine, A. H. SQUIRES (by invitation) and M. W. JOHNSTON (by invitation), Clinical Teachers, University of Toronto Faculty of Medicine.

3:00 **Military Psychiatry Today.**
FRANCIS J. BRACELAND, F.A.C.P., Professor of Psychiatry, University of Minnesota, Mayo Foundation, Rochester.

3:20 INTERMISSION.

3:40 **The Ranges of Usage of Streptokinase-Streptodornase in Military Medicine.**
WILLIAM S. TILLETT (by invitation), Professor of Bacteriology, New York University College of Medicine.

4:00 **Air Transportation of Cardiac and Pulmonary Patients.**
Major VINCENT M. DOWNEY, M.C. (Associate), and Lieutenant Colonel BENJAMIN A. STRICKLAND, JR., M.C. (Associate), United States Air Force.

4:20 **Radiation Injury Following an A-Bomb Explosion.**
Brigadier General ELBERT DECOURSEY, F.A.C.P., M.C., United States Army.

4:40 **Medical Problems in Radiological Defense.**
Commander FRANK R. PHILBROOK (by invitation), M.C., United States Navy.

5:00 ADJOURNMENT.

THIRD GENERAL SESSION

Opera House, Kiel Auditorium

Wednesday Afternoon, April 11, 1951

Presiding Officer
Reginald Fitz, F.A.C.P., Boston, Mass.

P.M.

2:00 **Further Observations on the Use of Liberal Diets in the Treatment of Diabetes Mellitus.**
HENRY J. JOHN, F.A.C.P., Cleveland.

2:30 **The Current Status of Antacid and Antisecretory Drugs.**
JOSEPH B. KIRSNER, F.A.C.P., Associate Professor of Medicine, University of Chicago School of Medicine.

2:50 **Pain in Acute and Chronic Diseases of the Liver.**
HOWARD P. LEWIS, F.A.C.P., Professor and Head of Department of Medicine, University of Oregon Medical School.

3:10 **The Use of Cation Exchange Resins in Clinical Situations.**
THADDEUS S. DANOWSKI, F.A.C.P., Renziehausen Professor of Research Medicine, University of Pittsburgh School of Medicine.

3:30 INTERMISSION.

3:50 **Iron Metabolism and the Therapy of Iron Deficient States.**
CARL V. MOORE, F.A.C.P., Professor of Medicine, Washington University School of Medicine.

4:10 **The Relationship of Vitamin B_{12} to the Intrinsic Factor of Castle.**
FRANK H. BETHELL, F.A.C.P., Professor of Internal Medicine, University of Michigan Medical School.

4:30 **Clinical and Laboratory Observations on Auto-Immune Hemolytic Disease.**
LAWRENCE E. YOUNG, F.A.C.P., Assistant Professor of Medicine, University of Rochester School of Medicine.

4:50 **Current Concepts of the Coagulation Mechanism.**
KENNETH M. BRINKHOUS (by invitation), Professor of Pathology, University of North Carolina School of Medicine.

5:10 ADJOURNMENT.

FOURTH GENERAL SESSION

Opera House, Kiel Auditorium

Thursday Afternoon, April 12, 1951

P.M.

2:00 THE ANNUAL BUSINESS MEETING.

All Fellows and Masters are urged to be present and to participate more actively in the administrative problems of the College. Reports will be received from the Secretary-General, Executive Secretary, and Treasurer; elections of new Officers, Regents and Governors will take place; President-Elect Maurice C. Pincoffs, M.A.C.P., of Baltimore, Md., will be inducted as President and will make a brief inaugural address.

2:40 INTERMISSION.

Presiding Officer
Marion A. Blankenhorn, F.A.C.P., Cincinnati, Ohio

3:00 **Animal Diseases of Public Health Importance.**
JAMES H. STEELE, V.M.D. (by invitation), Atlanta, Ga.

3:20 **New Problems in the Treatment of the Infectious Diseases.**
C. PHILLIP MILLER, F.A.C.P., Professor of Medicine, University of Chicago School of Medicine.

3:40 INTERMISSION.

4:00 **The Prevention of Rheumatic Fever.**
CHARLES H. RAMMELKAMP, JR. (by invitation), Assistant Professor of Preventive Medicine, Western Reserve University School of Medicine.

4:20 **What Is Chronic Brucellosis?**
WESLEY W. SPINK, F.A.C.P., Professor of Medicine, University of Minnesota Medical School.

4:40 **The Effect of Cortisone in the Treatment of Typhoid Fever.**
JOSEPH E. SMADEL (by invitation), Army Medical Center, Washington D. C.; THEODORE E. WOODWARD (by invitation), Associate Professor of Medicine, and ROBERT T. PARKER (by invitation), Fellow in Medicine, University of Maryland School of Medicine.

5:00 ADJOURNMENT.

FIFTH GENERAL SESSION

Opera House, Kiel Auditorium

Friday Afternoon, April 13, 1951

Presiding Officer
Walter L. Palmer, F.A.C.P., Chicago, Ill.

SYMPOSIUM ON THE INCREASING LIFE SPAN

P.M.

2:00 **A Biblical Introduction to Geriatric Medicine.**
LOUIS KRAUSE, F.A.C.P., Professor of Clinical Medicine, University of Maryland School of Medicine.

2:20 **Some Social Implications of Medical Progress.**
FRANK DICKINSON, Ph.D. (by invitation), Chicago.

2:40 **Rationale of Geriatric Medicine.**
EDWARD J. STIEGLITZ, F.A.C.P., Washington, D. C.

3:00 **Distribution of Proteins and Lipids in Atheroma.**
DAVID P. BARR, F.A.C.P., Professor of Medicine, Cornell University Medical College.

3:20 INTERMISSION.

3:40 **The Role of Elastic Tissue in the Formation of the Arteriosclerotic Lesion.**
ALBERT I. LANSING (by invitation), Research Fellow, Washington University School of Medicine.

4:00 **Who's Next with Myocardial Infarction?**
HENRY M. WINANS, F.A.C.P., Professor of Medicine and History of Medicine, Southwestern Medical School, University of Texas.

4:20 **Endocrine Patterns During Aging.**
THOMAS H. MCGAVACK, F.A.C.P., Professor of Clinical Medicine, New York Medical College.

4:40 **Revitalization of Tissue and Nutrition in Older Individuals.**
WILLIAM B. KOUNTZ (by invitation), Assistant Professor of Medicine, Washington University School of Medicine.

5:00 ADJOURNMENT.

MORNING LECTURES

The Morning Lectures recognize the increasing interest in fundamental problems and are planned to supplement the subject matter of the General Sessions. The Lectures enable the speaker to cover his presentation fully and to utilize charts, slides, motion pictures and other media to amplify his presentation.

Morning Lectures will be offered from 9:30 to 11:30, Wednesday and Friday mornings only. They are open to all members and guests of the College.

Admission by regular registration badge; no special tickets.

Wednesday, April 11, 1951

Opera House, Kiel Auditorium

Presiding Officer

Charles F. Moffatt, F.A.C.P., Montreal, Que., Canada

A.M.

9:30–10:20 **The Functional Interrelationship of the Anterior Pituitary and the Adrenal Cortex.**
DWIGHT INGLE, Ph.D. (by invitation), Kalamazoo, Mich.

10:20–10:40 INTERMISSION.

10:40–11:30 **The Clinical Application of Pituitary Adrenocorticotropic and of Adrenal Steroid Hormones.**
LAURANCE W. KINSELL, F.A.C.P., Associate Clinical Professor of Medicine, University of California.

Friday, April 13, 1951

Opera House, Kiel Auditorium

Presiding Officer

LeRoy H. Sloan, F.A.C.P., Chicago, Ill.

A.M.

9:30–10:00 **The Meeting Place for Industrial Health.**
DWIGHT O'HARA, F.A.C.P., Dean and Professor of Preventive and Industrial Medicine, Tufts College Medical School.

10:00–10:30 **Current Concepts of Beryllium Poisoning.**
H. SCOTT VANORSTRAND, F.A.C.P., Assistant Professor of Medicine, Frank E. Bunts Educational Institute, Cleveland Clinic Foundation, Western Reserve University School of Medicine.

10:30–11:00 **Phosphate Ester Poisoning, a New Problem for the Internist.**
DONALD O. HAMBLIN (by invitation), and JOHN H. F. MARCHAND (by invitation), New York, N. Y.

PANEL DISCUSSIONS

Topics of intimate interest and practical value to all members of the profession have been chosen. Qualified men have been selected as leaders and members of the panel personnel. All panels are scheduled from Tuesday through Friday, 12:00 noon to 1:15 P.M., and will be held in the Kiel Auditorium.

Application for tickets to all panels may be made in advance by members on the regular application form which will accompany the formal program and which will be sent to all members of the College. Tickets will also be available at the Registration Bureau, Kiel Auditorium.

Applicants may submit in writing three weeks before the Session, through the Executive Secretary of the College, any questions concerning any phase of the subjects listed. Moderators and panel personnel will answer those questions which they feel are applicable to the subject under discussion, and will answer as many questions as time permits.

SUMMARY OF PANEL DISCUSSIONS

Tuesday, April 10, 1951

I **Use of ACTH and Cortisone in Collagen Diseases.**
Moderator: *George Baehr, New York, N. Y.

II **Cardioangiography.**
Moderator: *W. Edward Chamberlain, Philadelphia, Pa.

III **Carcinoma of the Lung.**
Moderator: Evarts A. Graham, St. Louis, Mo.

IV **Pathogenesis of Atheromatosis.**
Moderator: *Irvine H. Page, Cleveland, Ohio.

V **Virus Diseases; Recent Developments.**
Moderator: Robert J. Huebner, Bethesda, Md.

Wednesday, April 11, 1951

VI **Antibiotics: Recent Advances.**
Moderator: John H. Dingle, Cleveland, Ohio.

VII **Chemotherapy of Neoplasms.**
Moderator: *Charles A. Doan, Columbus, Ohio.

VIII **Hemolytic Anemias.**
Moderator: *William Dameshek, Boston, Mass.

IX **Newer Treatment of Renal Disorders.**
Moderator: *Robert F. Loeb, New York, N. Y.

X **Valvulotomy: Indications, Preoperative and Postoperative Care.**
Moderator: C. Rollins Hanlon, St. Louis, Mo.

Thursday, April 12, 1951

XI **Rehabilitation of Paraplegics and Hemiplegics.**
Moderator: *Howard A. Rusk, New York, N. Y.

XII **Neuropsychiatric Effects of ACTH and Cortisone.**
Moderator: *Francis J. Braceland, Rochester, Minn.

XIII **Radio Isotopes in Medicine.**
Moderator: *Leon O. Jacobson, Chicago, Ill.

XIV **Blood Transfusion Problems.**
Moderator: *Elmer L. DeGowin, Iowa City, Iowa.

XV **Bacterial Allergy.**
Moderator: *Walter S. Burrage, Boston, Mass.

Friday, April 13, 1951

XVI **Electrocardiography: Current Problems.**
Moderator: *Gordon B. Myers, Detroit, Mich.

XVII **Tuberculosis: Prevention and Therapy.**
Moderator: *Julius L. Wilson, New Orleans, La.

XVIII **Insulins: Physiological and Clinical Effects.**
Moderator: *Joseph H. Barach, Pittsburgh, Pa.

XIX **Hemorrhage from the Upper Alimentary Tract.**
Moderator: *Leon Schiff, Cincinnati, Ohio.

XX **Hormonal Treatment of Pemphigus and Allergic Dermatoses.**
Moderator: *Arthur C. Curtis, Ann Arbor, Mich.

*F.A.C.P.

Note: Participants in the above panels will be announced in the official program which will be mailed to all members of the College.

THE CLINIC SESSIONS

Color Television of Medical Clinics

The following series of clinics will be televised in color on Tuesday, Wednesday, Thursday and Friday mornings between 9:30 A.M. and 11:30 A.M. from the St. Louis City Hospital by a group of physicians from participating hospitals and medical schools.

Due to changing programs, from one clinic to another, a slight lag may occur. However, it is believed that times indicated will be approximately correct.

Admission by regular badge; no special tickets required.

Tuesday, April 10, 1951

9:30– 9:40 **The Use of Streptokinase and Streptodornase.**

WILLIAM S. TILLETT (by invitation), Professor of Medicine, New York University College of Medicine; WILLIAM PERRY (by invitation), Assistant in Medicine, Barnes Hospital, Washington University School of Medicine; and JOSEPH MUENSTER (by invitation), Assistant Resident in Medicine, St. Louis City Hospital.

9:45– 9:55 **Post-Pneumonectomy Respiratory Function.**

EVARTS A. GRAHAM, F.A.C.S. (by invitation), Professor of Surgery, Washington University School of Medicine; RICHARD M. PETERS (by invitation), Fellow in Thoracic Surgery, Washington University School of Medicine; and ALBERT ROOS (by invitation), Instructor in Surgery and Physiology, Washington University School of Medicine.

10:00–10:10 **Resection for Pulmonary Tuberculosis.**

ISRAEL J. FLANCE (Associate), Instructor in Clinical Medicine, Washington University School of Medicine.

10:15–10:25 **Respiratory Function Studies.**

HERBERT C. SWEET (Associate), Instructor in Medicine, St. Louis University School of Medicine.

10:30–10:40 **Esophageal Tamponade for Control of Bleeding Varices.**

BRUCE D. KENAMORE, F.A.C.P., Associate Professor of Clinical Medicine, Washington University School of Medicine; GLADDEN V. ELLIOTT (by invitation), Instructor in Radiology, Washington University School of Medicine; and LEON SCHIFF, F.A.C.P., Associate Professor of Medicine, University of Cincinnati College of Medicine.

10:45–10:55 **Clinical Evaluation of Portocaval Shunt Operations.**

L. V. MULLIGAN (by invitation), Assistant Professor of Clinical Surgery, St. Louis University School of Medicine.

11:00–11:10 **The Localization of Intracranial Neoplasms with Radioactive Diiodofluorescein.**

ROBERT DEAN WOOLSEY (by invitation), Instructor in Surgery, St. Louis University School of Medicine, and GEORGE E. THOMA (by invitation), Resident in Medicine, Firmin Desloge Hospital, St. Louis University School of Medicine.

11:15–11:30 **Tumor Conference.**

CHARLES L. ECKERT (by invitation), Assistant Professor of Surgery, Washington University School of Medicine; LAUREN V. ACKERMAN (by invitation), Associate Professor of Surgical Pathology and Pathology, Washington University School of Medicine; EUGENE M. BRICKER, F.A.C.S. (by invitation), Associate Professor

of Clinical Surgery, Washington University School of Medicine; WILLIAM B. SEAMAN (by invitation), Instructor in Radiology, Washington University School of Medicine; and EDWARD H. REINHARD (by invitation), Associate Professor of Medicine, Washington University School of Medicine.

Wednesday, April 11, 1951

9:30– 9:45 **Hyperventilation Syndrome—Psychiatric Evaluation.**
GEORGE SASLOW (by invitation), Associate Professor of Psychiatry in Department of Medicine, Washington University School of Medicine, and EDWIN F. GILDEA (by invitation), Professor of Neuropsychiatry, Washington University School of Medicine.

9:50–10:05 **Electro-Shock Therapy.**
ERNEST H. PARSONS, F.A.C.P., Assistant Professor of Clinical Psychiatry, Washington University School of Medicine.

10:10–10:25 **Application of Electro-encephalography in Clinical Medicine.**
JAMES L. O'LEARY (by invitation), Professor of Neurology, Washington University School of Medicine, and WARREN MILLS (by invitation), Acting Director, Bliss Psychopathic Hospital, St. Louis.

10:30–10:45 **The Lupus Erythematosis Phenomenon.**
RICHARD S. WEISS (by invitation), Professor of Clinical Dermatology, Washington University School of Medicine; SETH S. BARNES (by invitation), Assistant in Clinical Dermatology, Washington University School of Medicine; and GEORGE BAEHR, F.A.C.P., Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, and Chairman, Board of Directors, Health Insurance Plan of Greater New York.

10:50–11:05 **Contact Dermatitis.**
STANLEY F. HAMPTON (by invitation), Instructor in Clinical Medicine, Washington University School of Medicine.

11:10–11:30 **Dermatologic Cases of Medical Interest.**
GAROLD V. STRYKER (by invitation), Professor of Dermatology and Syphilology, St. Louis University School of Medicine.

Thursday, April 12, 1951

9:30– 9:45 **Malignant Exophthalmos.**
DANIEL L. SEXTON, F.A.C.P., Assistant Clinical Professor of Medicine, St. Louis University School of Medicine.

9:50–10:05 **Radio-Iodine in Thyroid Disease.**
LEO GOTTLIEB (by invitation), Assistant Professor of Clinical Medicine, Washington University School of Medicine.

10:10–10:25 **The Flame Photometer as Applied to Clinical Problems.**
ROBERT ELMAN, F.A.C.S. (by invitation), Professor of Surgery, Washington University School of Medicine, and THEODORE E. WEICHSELBAUM, Ph.D. (by invitation), Department of Surgery, Washington University School of Medicine.

10:30–10:45 **Iliac Marrow Aspiration in Hematologic Disorders.**
RAYMOND O. MUETHER, F.A.C.P., Associate Professor of Internal Medicine, St. Louis University School of Medicine, and CHARLES A. DOAN, F.A.C.P., Dean and Professor of Medicine, Ohio State University College of Medicine.

10:50–11:05 **Recent Progress in the Therapy of Hematologic Disorders.**
EDWARD H. REINHARD (by invitation), Associate Professor of Medicine, Washington University School of Medicine, and CARL V. MOORE, F.A.C.P., Professor of Medicine, Washington University School of Medicine.

11:10–11:30 **Rehabilitation of the Deaf and Speech Defective Person.**
S. RICHARD SILVERMAN, Ph.D. (by invitation), Director, Central Institute for the Deaf, St. Louis.

Friday, April 13, 1951

9:30– 9:40 **Examination of the Back.**
ROBERT M. O'BRIEN (by invitation), Professor of Orthopedic Surgery, St. Louis University School of Medicine.

9:45–10:00 **Physical Treatment in Internal Medicine.**
SEDGWICK MEAD (by invitation), Assistant Professor of Physical Medicine, Washington University School of Medicine.

10:05–10:15 **A Simplified Mannikin for Teaching Congenital Heart Disease.**
ARMAND E. BRODEUR (by invitation), Graduate Fellow in Radiology, St. Mary's Group of Hospitals, St. Louis University School of Medicine.

10:20–10:40 **Symposium on Congenital Heart Disease.**
CHESTER P. LYNXWILER (by invitation), Instructor in Pediatrics, St. Louis University School of Medicine; SIDNEY SMITH (by invitation), Assistant Professor of Surgery, St. Louis University School of Medicine; and DON C. WEIR (by invitation), Assistant Clinical Professor of Radiology, St. Louis University School of Medicine.

10:45–10:55 **Peripheral Vascular Diseases.**
JOSEPH C. EDWARDS, F.A.C.P., Instructor in Clinical Medicine, Washington University School of Medicine, and PETER HEINBECKER (by invitation), Professor of Clinical Surgery, Washington University School of Medicine.

11:00–11:10 **An Evaluation of Khellin as a Coronary Vasodilator.**
DAVID B. FLAVAN, F.A.C.P., Assistant Professor of Clinical Medicine, St. Louis University School of Medicine.

11:15–11:25 **Dolomine Injection of Stellate Ganglion in Angina Pectoris.**
JAMES B. STUBBS (Associate), Instructor in Internal Medicine, St. Louis University School of Medicine; HAROLD J. FREIHEIT (by invitation), Instructor in Surgery and Head of Department of Anaesthesiology, St. Louis University School of Medicine; and HENRY M. WINANS, F.A.C.P., Professor of Medicine and History of Medicine, Southwestern Medical School of The University of Texas, Dallas.

CLINICS AT HOSPITALS

The regular Hospital Clinics will be conducted on Tuesday and Thursday, from 9:15 A.M. to 11:30 A.M., whereas Morning Lectures will be conducted on Wednesday and Friday mornings, thus eliminating competition between these features of the program.

Adequate accommodations are available, but **admission to the Hospital Clinics will require special tickets,** which will be issued to MEMBERS in advance of the Session, and to NON-MEMBERS directly at the Registration Bureau in the Kiel

Auditorium. Application forms for tickets for the Clinics and Panel Discussions will accompany the final program to all members.

Emphasis will be placed on clinics in the true sense of that term—that is, patients will be shown and discussed, rather than having presentations of formal short papers. A wide range of medical topics important to the clinician is offered. Visitors have the opportunity to see patients at close range and to observe hospital methods in St. Louis.

All clinics must terminate promptly at 11:30 A.M., in order that members may have adequate time to reach the Panel Discussions, which start at 12:00 M.

The Committee on Transportation recommends the use of taxicabs for reaching the Hospital Clinics, and has arranged that there shall be an adequate number of taxicabs available, not only for the trip to the clinics, but also for the return trip.

Tickets will be required for each and every one of the Hospital Clinics, unless specifically otherwise mentioned. The coöperation of everyone in securing his Clinic Tickets will assist greatly in distributing the attendance according to the capacity of each meeting room. It is self-evident that a clinic arranged for fifty will lose its value for all if a hundred are present. Ticket registration, naturally, is the only effective method of keeping the attendance within the capacity indicated.

PROGRAM OF HOSPITAL CLINICS

Tuesday, April 10, 1951

A

BARNES HOSPITAL

(600 South Kingshighway Blvd.)

(Capacity, 200)

9:15 The Management of Acute Bacterial Pneumonia.
W. Barry Wood, Jr.

9:35 Treatment of Subacute Bacterial Endocarditis.
Thomas H. Hunter.

9:55 Non-allergic Asthma.
Harry L. Alexander.

10:15 Recess.

10:30 Diagnosis of Bronchogenic Carcinoma.
Evarts A. Graham.

11:00 Multiple Myeloma.
David P. Barr, New York.

B

ST. LUKE'S HOSPITAL

(5535 Delmar Blvd.)

(Capacity, 100)

9:15 Problems in the Interpretation of V Leads.
Julius Jensen.

9:35 Modified Insulin and the Treatment of Diabetes.
Cyril M. MacBryde.

9:55 Treatment of Bleeding Esophageal Varices.
Bruce D. Kenamore.

10:15 Recess.

10:30 Dermatological Clinic.
Richard S. Weiss.

10:50 Aortic Stenosis.
William B. Bean, Iowa City.

C **ST. LOUIS CITY HOSPITAL**

St. Louis University Service

(1515 Lafayette Ave.)

(Capacity, 200)

9:15 Eosinophilic Granuloma.
Paul Murphy and William H. Bauer.
9:35 Pulmonary Emphysema and Pulmonary Fibrosis.
Herbert C. Sweet.
9:55 Pathogenesis and Treatment of Cor Pulmonale.
Richard V. Ebert, Minneapolis.
10:30 Recess.
10:40 Hypersplenism.
Charles A. Doan, Columbus.
11:10 The Management of Myocardial Infarction.
John J. Hammond.

D **ST. LOUIS CITY HOSPITAL**

Washington University Service

(1515 Lafayette Ave.)

(Capacity, 200)

9:15 The Mechanism of Removal from the Circulation of Abnormal Cells in Leukemia.
Howard R. Bierman, San Francisco.
9:35 Jarisch-Herxheimer Reaction in the Penicillin Treatment of Syphilis.
Virgil C. Scott.
9:55 Pseudo-Cushing's Syndrome.
Henry A. Schroeder.
10:15 Recess.
10:30 Etiologic Factors in Acute Rheumatic Fever.
Robert J. Glaser.
10:50 Enzymatic Treatment of Empyema.
William S. Tillett, New York.

E **FIRMIN DESLOGE HOSPITAL**

(1325 S. Grand Blvd.)

(Capacity, 200)

9:15 Subacute Bacterial Endocarditis.
Ralph A. Kinsella, Sr.
9:35 Cirrhosis of the Liver.
a. Biochemistry.
Edward A. Doisy, Jr.
b. Medical Aspects.
G. O. Broun.
c. Surgical Therapy.
Harry K. Purcell.
10:15 Recess.

10:30 Diagnostic Aspects of Atypical Pneumonia.
Raymond O. Muether.
11:00 Anticoagulant Therapy—Old and New.
Edgar V. Allen, Rochester, Minn.

F

MISSOURI BAPTIST HOSPITAL

(919 N. Taylor Ave.)

(Capacity, 150)

9:15 Metabolic Changes Occurring During the Treatment of Cardiac Failure.
Grace E. Bergner.
9:35 The Diagnosis and Management of Osteoporosis.
Truman G. Drake, Jr.
9:55 The Management of Diabetic Neuritis.
Ray D. Williams.
10:15 Recess.
10:30 Infectious Hepatitis.
Richard B. Capps, Chicago (pending).
11:00 Arteriosclerotic Heart Disease.
Hugh J. Morgan, Nashville.

G

JEWISH HOSPITAL

(216 S. Kingshighway Blvd.)

(Capacity, 300)

9:15 Histoplasmosis.
Alfred Goldman.
9:35 Dissecting Aneurysm.
Llewellyn Sale, Sr.
9:55 Collagen Disease.
George Baehr, New York.
10:15 Recess.
10:30 Symposium on Pancreatitis.
Carl J. Heifetz, H. T. Blumenthal and K. Kinsella.

(COMBINED PROGRAM)

Evangelical Deaconess Hospital and
Veterans Administration Hospital, Jefferson Barracks, Missouri
at

H

EVANGELICAL DEACONESS HOSPITAL

(6150 Oakland Ave.)

(Capacity, 300)

9:15 Psychosomatic Aspects of Peptic Ulcer.
George Saslow.
9:35 The Management of Cardiac Disturbances Following Pneumonectomy.
Edward Massie.
9:55 Virus Encephalitis.
Ernest T. Rouse, Jr.
10:15 Recess.

10:30 Acute Bacterial Arthritis.
Marion A. Blankenhorn, Cincinnati.
11:00 Congestive Heart Failure.
Tinsley R. Harrison, Birmingham (pending).

Thursday, April 12, 1951

A

BARNES HOSPITAL

(600 S. Kingshighway Blvd.)

(Capacity, 200)

9:15 Therapeutic Implications of Current Concepts of Sickle Cell Disease.
Carl V. Moore.
9:35 The Handling of First Convulsive Seizures in Adults.
James L. O'Leary.
9:55 Use of the Sex Steroids in Treating the Menopause.
Willard M. Allen.
10:15 Recess.
10:30 Fundamental Mechanisms of Cardiospasm.
Albert I. Mendeloff.
10:50 Mesenchymal Tumors of the Stomach.
Gladden V. Elliott and Hugh M. Wilson.
11:10 Treatment of Thyrotoxicosis.
William H. Daughaday.

B

ST. LUKE'S HOSPITAL

(5535 Delmar Blvd.)

(Capacity, 100)

9:15 Current Therapy in Rheumatoid Arthritis.
Paul O. Hagemann.
9:35 Rehabilitation Problems of Clinical Medicine.
Howard A. Rusk, New York.
10:45 Recess.
11:00 Medical Management of Hyperthyroidism.
Robert H. Williams, Seattle.

C

ST. LOUIS CITY HOSPITAL

St. Louis University Service

(1515 Lafayette Ave.)

(Capacity, 200)

9:15 The Treatment of Shock in Myocardial Infarction.
James G. Janney, Jr.
9:35 Pancreatic Atrophy: The Diagnosis and Treatment.
William A. Knight, Jr., Theodore L. Bryan and Melvin Casberg.
9:55 Management of Peptic Ulcer.
Walter L. Palmer, Chicago.
10:30 Recess.

10:40 Surgical Management of Portal Hypertension.
L. V. Mulligan.
11:00 Hypopituitarism.
Daniel L. Sexton.

D

ST. LOUIS CITY HOSPITAL

Washington University Service

(1515 Lafayette Ave.)

(Capacity, 200)

9:15 Pulmonary Embolism: Its Physiologic Implications.
John R. Smith.
9:35 Mechanism of Insulin-resistant Diabetes.
Charles R. Park.
9:55 Newer Aspects of Homologous Serum Jaundice.
Robert E. Shank.
10:15 Recess.
10:20 Medical Therapy of Urinary Tract Infections.
Carl G. Harford.
10:40 Drug Allergy.
Samuel C. Bukantz.
11:00 Brucellosis.
Wesley W. Spink, Minneapolis.

E

FIRMIN DESLOGE HOSPITAL

(1325 S. Grand Blvd.)

(Capacity, 200)

9:15 Diagnosis and Localization of Brain Tumors by Radioisotopes.
Robert Dean Woolsey and George E. Thoma.
9:35 Surgical Treatment of Heart Disease.
C. Rollins Hanlon.
9:55 Panhypopituitarism: Some Aspects of Carbohydrate Metabolism.
Ralph A. Kinsella, Jr., and Willard O. Thompson, Chicago.
10:25 Recess.
10:40 Therapy of Peptic Ulcer.
Leslie D. Cassidy.
11:00 Infections of the Respiratory Tract.
Maxwell Finland, Boston (pending).

F

MISSOURI BAPTIST HOSPITAL

(919 N. Taylor Ave.)

(Capacity, 150)

9:15 The Surgical Treatment of Hypertension.
Roland S. Kieffer.
9:35 Secondary Hypersplenism.
Edward H. Reinhard.

9:55 Diverticulitis Coli.
John L. Horner.
10:15 Recess.
10:30 Hiatus Hernia.
Samuel B. Grant.
10:50 Thrombocytopenic Purpura.
W. Harrington.

G

JEWISH HOSPITAL

(216 S. Kingshighway Blvd.)

(Capacity, 300)

9:15 Unresolved Pneumonia.
Israel J. Flance.
9:35 The Chemotherapy of Pulmonary Tuberculosis.
Llewellyn Sale, Jr.
9:55 The Use and Misuse of Punch Biopsies of the Liver.
Michael M. Karl.
10:15 Recess.
10:30 Bone Tumors—Radiologic Diagnosis.
H. R. Senturia and L. J. Fox.
11:00 Disturbances in Potassium Metabolism.
Thaddeus S. Danowski, Pittsburgh (pending).

H

(COMBINED PROGRAM)

Evangelical Deaconess Hospital and
Veterans Administration Hospital, Jefferson Barracks, Missouri
at
EVANGELICAL DEACONESS HOSPITAL

(6150 Oakland Ave.)

(Capacity, 300)

9:15 Surgical Treatment of Pulmonary Disease.
James L. Mudd.
9:35 Asymptomatic Myocarditis.
Robert C. Kingsland.
9:55 Pulmonary Osteoarthropathy.
Don C. Weir.
10:15 Recess.
10:30 The Relation of Streptococcal Infection to Rheumatic Fever.
Charles H. Rammelkamp, Jr., Cleveland.
11:00 The Management of Rheumatoid Arthritis.
Philip S. Hench, Rochester, Minn. (pending).